

ACTA OPHTHALMOLOGICA

A K K LUNDGAARD EDI COEPTA

Redactores

Dania POUL BRÆNDSTRUP EILIF GREGERSEN VIGGO A JENSEN
HANS WALTHER LARSEN POUL MARTIN MØLLER

Fennia HENRIK FORSIUS ARVO OKSALA SALME VANNAS

Islandia ULFAR THORDARSON

Norvegia ARVID ANSETH TORSTEIN BERTELSEN

HANS PETER PFIFERSEN THORLIE THOMASSEN JAN YTTÉBORG

Suetia GUNNAR v. BAHR ARNE HUGGERT GUSTA KARPE

TORSTEN KRAKAU ERIK LINNÉR SVEN ERIK NILSSON

ERIK PALM GÖTE ÖSTERLIND

Editor

POUL BRÆNDSTRUP COPENHAGEN

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THE LONGITUDINAL HOROPTER IN A CASE OF CONCOMITANT STRABISMUS WITH ANOMALOUS CORRESPONDENCE

BY

ULF HALLDÉN

The retinal correspondence was measured at several points of the binocular visual field in a case of anomalous correspondence. It was found that the anomalous correspondence was not limited to the foveae but that there were pairs of peripheral anomalously corresponding points. The angle of anomaly was not constant over the binocular field. The correspondence was reciprocal at some points, non-reciprocal at others. A comparison was made between normal and anomalous correspondence and the learning of anomalous correspondence was discussed.

Key words: strabismus - normal correspondence - anomalous correspondence - horopter - diplopia - reinforcement - conditioning

Our visual impressions arrange themselves into coherent pictures because each retinal element has a certain spatial value. A large part of the field of vision is common to both eyes. As far as this part is concerned, two retinal elements, one in each eye, have the same spatial value. There is a large number of such pairs of elements with the same spatial value. A stimulus affecting one element in such a pair will be localised in the same direction as if it had affected the other. This common visual direction is characteristic of corresponding visual elements or more briefly, corresponding points.

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Normal correspondence is characterised primarily by the fact that both foveae are corresponding points. This is not sufficient as a definition of normal correspondence. In general it may be said that in normal correspondence the corresponding points are distributed over the retinae in a normal way. This distribution can be studied by determining the horopter. The horopter is defined as the locus of points in space whose images fall on corresponding points of the two retinae.

An erroneous relative position of the eyes causes corresponding retinal points to receive different images. It also causes disparate (non corresponding) retinal points to receive identical stimuli. Those two aspects of the same thing are called respectively confusion and diplopia.

In concomitant strabismus confusion and diplopia are avoided by a number of mechanisms. Most important among those are suppression and anomalous correspondence.

On the basis of anomalous correspondence there is a certain degree of binocular vision. There are pairs of (anomalously) corresponding points and if there is a point in space whose retinal images fall on such a pair of corresponding points this point in space is situated on the horopter. This horopter of anomalous correspondence is one of common visual directions comparable to the nonius horopter of Tschermak (1931) and Shipley & Rawlings (1970).

The apparent frontal plane horopter of Hering is more generally known than the nonius horopter and has had a more wide spread use. In normal binocular vision the apparent frontal plane is easier to measure than the nonius horopter. The apparent frontal plane is probably not a true horopter but in approximation however we have reasons both theoretical and empirical for believing that it is a good approximation.

Bagolini & Capobianco (1965) and Pasino & Maraini (1966) have attempted to study the horopter in strabismus with anomalous correspondence by the apparent frontal plane method. In this way it was possible to measure the limits of areas of binocular single vision. Outside those limits there was diplopia or sometimes suppression. It is impossible to determine the position of the apparent frontal plane however as stereoscopic vision is absent.

One point on the normal horopter has a special significance: the point of fixation. The retinal images of the point of fixation fall on the two foveae. On the horopter of anomalous correspondence two points have such a special significance. In an earlier communication (Hallden 1952) I called those two points N_1 and N . One of the retinal images of the point N_1 falls on the fovea of the fixing eye, the other on a point in the periphery of the retina of the squinting eye. This peripheral retinal point corresponds to the fovea of the fixing eye. If the point N_1 coincides with the point of fixation, the angle of

squint is compensated by the angle of anomaly and the anomalous correspondence is harmonious in this part of the binocular field. The retinal images of the point N fall on another pair of interesting corresponding points: the fovea of the squinting eye and a point in the periphery of the fixing eye. At the point N there is harmony if the angle of anomaly is equal to the angle of squint.

The quality of binocular vision achieved by anomalous correspondence is determined to a considerable degree by harmony at the points N_1 and N because a diplopia in which one of the images is foveal or a confusion between foveal images is extremely disturbing. It is therefore usual to limit the study of binocular vision in anomalous correspondence to measurement of the harmony at those two points or in many publications at point N_1 only.

It is possible that anomalous correspondence is confined to those regions of the binocular field where foveal vision is involved. In purely non foveal vision it might be easy to disregard confusion and diplopia or to suppress unwanted images.

For this reason it is interesting to measure the correspondence at several points of the binocular field. Such measurements are time consuming and for the observer rather difficult; therefore the present study has been limited to only one subject.

The Observer

Male 19 years. Alternating squint since early childhood. The angle of squint seems to have been about 20° in childhood. About puberty when he started wearing glasses the angle diminished. The right eye has always been dominant but there was no amblyopia and no treatment by occlusion. Never operated.

Visual acuity. Objective angle eso 9°, subjective angle exo 1°. Little suppression. No diplopia could be provoked with coloured filters and prisms. With the Maddox rod, diplopia approximately equivalent to harmonious anomalous correspondence.

$$\begin{array}{l} \text{R.E. } +1.0 \text{ sph} \\ \text{L.E. } +1.0 \text{ sph} \end{array}$$

P.D. 5 mm.

The correspondence was purely anomalous: no vestiges of normal correspondence could be elicited. The objective angle of squint, the angle of

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The apparent frontal plane horopter of Hering is more generally known than the nonius horopter and has had a more wide spread use. In normal binocular vision the apparent frontal plane is easier to measure than the nonius horopter. The apparent frontal plane is probably not a true horopter but an approximation; however we have reasons both theoretical and empirical for believing that it is a good approximation.

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Synoptoscope Objective angle eso 8° ; subjective angle exo 1° . Little suppression. No diplopia could be provoked with coloured filters and prisms. With the Maddox rod diplopia approximately equivalent to harmonious anomalous correspondence.

$$V \quad R.E. 10 (+2.5 \text{ sph}) = 10$$

$$L.E. 10 (+1.5 \text{ sph}) = 10$$

$$P.D. = 57 \text{ mm}$$

The correspondence was purely anomalous; no vestiges of normal correspondence could be elicited. The objective angle of squint, the angle of

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give a circular spot of light invisible to the fixing eye but visible to the squinting eye. The cross and the spot were so different that no fusion between them was possible. This was verified by tests on persons with normal binocular vision as well as on the subject.

The cross was placed at a pre-determined distance from the point of fixation. The spot of light was moved until the observer indicated that it appeared to coincide with the centre of the cross. The distance of the light spot from the cross is a measure of the subjective angle in this part of the binocular field of vision. If the spot of light was on the same side of the cross as the squinting eye the subjective angle was given a negative sign (divergent relative to normal convergence); if it was at the opposite side of the cross the sign was positive.

With the right eye fixing, determinations were performed at seven points of the binocular field. At each of those points 22 readings were made and the S.D. was calculated to verify that the error of measurement was small.

When the left eye was fixing the measurements were equally precise but the observer was soon tired and had to rest. The number of readings at each point was limited to 16.

Results

The results are presented in Fig. 1A and B.

On the horizontal axes are given the positions in the binocular field. The zero line connects the fixing eye with the point of fixation. The angles are positive in the right half of the visual field, negative in the left. The vertical axes give the angles studied. The arithmetic means of the subjective angles are shown by small crosses. Around each cross is drawn a circle. The radius of this is four times the standard error of the mean. The angles of anomaly (dots) were calculated from the objective angle and the subjective angles measured. In Fig. 1A the angle of anomaly directly measured is plotted as a larger cross. It agrees perfectly with the curve for the calculated angle of anomaly.

The diagrams show that anomalous correspondence is not a purely foveal phenomenon limited to points N_1 and N . There are pairs of anomalously corresponding points in the periphery and consequently a kind of horopter. A horopter curve has been calculated from the measurements but is not reproduced because it gives no new information and because small errors of measurement of the angles will sometimes result in large errors in the positions of the points on the horopter curve.

anomaly at N and the subjective angle at N_1 were measured by the methods described in an earlier publication (Hallden 1952)

With the right eye fixing the mean value of the objective angle was $5^{\circ} 91$ eso. The number of measurements n was 46 and the standard deviation SD was $0^{\circ} 76$. The angle of anomaly at N_2 was $9^{\circ} 72$ $n = 46$ $SD = 0^{\circ} 69$.

The objective angle and the angle of anomaly are not constant they are variables and there is a co variation between them. The errors of measurement are small and the greater part of the SD is caused by the variations. The subjective angle at N_1 was $0^{\circ} 15$ exo $n = 59$ $SD = 0^{\circ} 20$. In this case there is harmony at N_1 but a distinct lack of harmony at N_2 . That means that the angle of anomaly is not equal all over the binocular field it is more than 2° larger at N than at N_1 . Such a discrepancy is not uncommon but the difference in this case is unusually large. This is one of the reasons why this case was chosen for a study of the horopter. With the left eye fixing it was not possible to measure the angle of anomaly at N because of suppression. The objective angle could be measured with difficulty and was about 6° . The subjective angle at N_1 was $0^{\circ} 38$ eso $n = 16$ $SD = 0^{\circ} 15$.

The Method Used to Measure the Horopter

An aluminized projection screen was used for the measurements. One property of such a screen is that it reflects polarised light diffusely but without causing any important change in the polarisation. The screen was provided with a fixation point. The observer was placed in front of the screen with his head in a stand which had a chin support. The distance from the eyes of the observer to the screen was two metres. A trial frame was fixed to the stand. In this frame were polaroids mounted in such a way that the axes of polarisation were at right angles to one another. Two projectors were used each provided with a rotatable polaroid. The images projected onto the screen could thus be extinguished for either of the eyes of the observer. The examinations were carried out in a room with good artificial lighting from unpolarised lamps. The observer was able to see equally well with each eye the fixation point the projection screen and a good deal of the surroundings of the screen. In this way the examinations could be performed under conditions as nearly similar as possible to those of free binocular vision and ordinary stimuli to fusion could be preserved. One of the two projectors made on the screen the image of a cross which was rendered invisible to the squinting eye by means of polarisation although it was visible to the fixing eye. The other projector was used to

give a circular spot of light invisible to the fixing eye but visible to the squinting eye. The cross and the spot were so different that no fusion between them was possible. This was verified by tests on persons with normal binocular vision as well as on the subject.

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Results

The results are presented in Fig. 1A and B.

On the horizontal axes are given the positions in the binocular field. The zero line connects the fixing eye with the point of fixation. The angles are positive in the right half of the visual field, negative in the left. The vertical axes give the angles studied. The arithmetic means of the subjective angles are shown by small crosses. Around each cross is drawn a circle. The radius of this is four times the standard error of the mean. The angles of anomaly (dots) were calculated from the objective angle and the subjective angles measured. In Fig. 1A the angle of anomaly directly measured is plotted as a larger cross. It agrees perfectly with the curve for the calculated angle of anomaly.

The diagrams show that anomalous correspondence is not a purely foveal phenomenon limited to points N_1 and N . There are pairs of anomalously corresponding points in the periphery and consequently a kind of horopter. A horopter curve has been calculated from the measurements but is not reproduced because it gives no new information and because small errors of measurement of the angles will sometimes result in large errors in the positions of the points on the horopter curve.

anomaly at N and the subjective angle at N_1 were measured by the methods described in an earlier publication (Hallden 1952)

With the right eye fixing the mean value of the objective angle was $5^\circ 91$ eso. The number of measurements n was 46 and the standard deviation SD was $0^\circ 76$. The angle of anomaly at N was $8^\circ 72$ $n=46$ $SD = 0^\circ 69$.

The objective angle and the angle of anomaly are not constant they are variables and there is a co variation between them. The errors of measurement are small and the greater part of the SD is caused by the variations. The subjective angle at N_1 was $0^\circ 15$ exo $n=53$ $SD = 0^\circ 20$. In this case there is harmony at N_1 but a distinct lack of harmony at N. That means that the angle of anomaly is not equal all over the binocular field it is more than 2° larger at N than at N_1 . Such a discrepancy is not uncommon but the difference in this case is unusually large. This is one of the reasons why this case was chosen for a study of the horopter. With the left eye fixing it was not possible to measure the angle of anomaly at N because of suppression. The objective angle could be measured with difficulty and was about 6° . The subjective angle at N_1 was $0^\circ 38$ eso $n=16$ $SD = 0^\circ 15$.

The Method Used to Measure the Horopter

An aluminized projection screen was used for the measurements. One property of such a screen is that it reflects polarised light diffusely but without causing any important change in the polarisation. The screen was provided with a fixation point. The observer was placed in front of the screen with his head in a stand which had a chin support. The distance from the eyes of the observer to the screen was two metres. A trial frame was fixed to the stand. In this frame were polaroids mounted in such a way that the axes of polarisation were at right angles to one another. Two projectors were used each provided with a rotatable polaroid. The images projected onto the screen could thus be extinguished for either of the eyes of the observer. The examinations were carried out in a room with good artificial lighting from unpolarised lamps. The observer was able to see equally well with each eye the fixation point the projection screen and a good deal of the surroundings of the screen. In this way the examinations could be performed under conditions as nearly similar as possible to those of free binocular vision and ordinary stimuli to fusion could be preserved. One of the two projectors made on the screen the image of a cross which was rendered invisible to the squinting eye by means of polarisation although it was visible to the fixing eye. The other projector was used to

Near the point N_1 the subjective angle is very small and the angle of anomaly is equal to the objective angle of squint the anomalous correspondence is harmonious. On both sides of the point N_1 the angles of anomaly increase and the subjective angles are increasingly negative (divergent). This increase of the angle of anomaly seems to be continuous without sudden jumps.

Anomalous correspondence develops in early childhood and at that age our subject had a larger angle of squint than he has now. It is probable that originally the angle of anomaly was equal to the objective angle. When the angle of squint diminished the adaptation of the angle of anomaly was only partial. At the point N_2 which is the most important part of the binocular field of vision perfect harmony was achieved but in more peripheral parts the angle of anomaly remained larger than the objective angle (cf. Moncrieff 1929).

FIG. 2

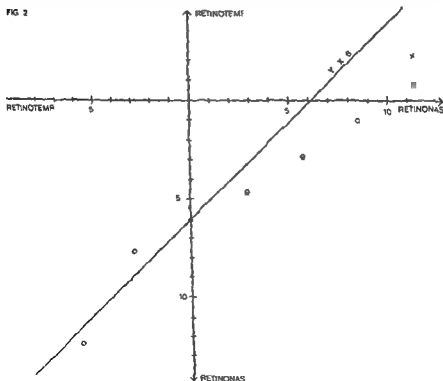


Fig. 2

The abscissa gives the positions of retinal points in the fixing eye the ordinate those of the corresponding points in the squinting eye. Thus each pair of corresponding points is represented by one point in the diagram. Values with R.F. fixing are plotted as circles, I.F. fixing as crosses.

FIG 1A

RIGHT EYE FIXING

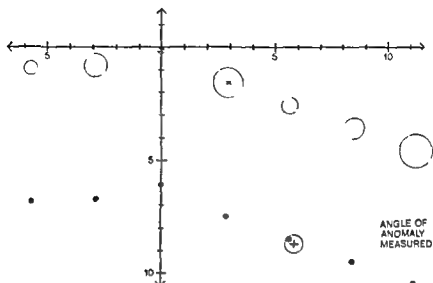


FIG 1B

LEFT EYE FIXING

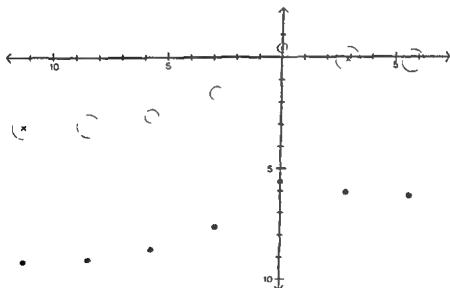


Fig 1A and B

The abscissae give the positions in the binocular field of vision positive angles in the right half negative in the left. The ordinates give the angles studied. The subjects' angles are shown by small crosses. The radius of the circle around each cross is four times the standard error of the mean. The angles of anomaly calculated are shown by dots. In Fig 1A the angle of anomaly directly measured at N is plotted as a larger cross.

With normal correspondence fusional movements can be elicited regularly and reproducibly. Fusional movements do occur with anomalous correspondence (Hallden 1952) but not regularly and there is no steady relationship between the fusional stimulus and resulting movement.

With normal correspondence temporary cooperation of horizontally disparate elements within Panum's areas provide stereopsis. This sensory fusion (Werner 1947) might be comparable to the fusional changes of the angle of anomaly which can be provoked by prisms (Halldén 1952) or sometimes occur after surgical correction of strabismus.

In anomalous as well as in normal correspondence binocular colour mixture, retinal rivalry and binocular contrast have been observed (Sachs 1897, Tschermak 1899, Braun 1978).

Thus there are similarities and differences between normal and anomalous correspondence. The similarities can be explained by comparable functions: the patient with anomalous correspondence avoids confusion and diplopia by achieving binocular single vision. The differences might be more fundamental.

Normal correspondence is possibly innate. If not it is at least founded on an anatomical basis of pre-formed pathways which gives a rigid point-to-point relationship between the retinal stimulus and cortical representation. No such pre-formed pathways are available for anomalous correspondence; the anatomical basis of which is the numerous synaptic relations of the cells of the cortex cerebri and the almost unlimited possibilities of intracortical association. Each of those cells has the potentiality of learning by facilitation or inhibition of connections. Faulty position of the eyes causes retinal points which would normally correspond to receive simultaneously quite different stimuli. The resulting confusion is avoided by inhibition of normal correspondence. It also causes retinal points which would not normally correspond to receive identical stimuli. This would give diplopia which is avoided by facilitation of the relevant connections to lead to the development of anomalous correspondence.

Anomalous correspondence is acquired by learning. It might be useful to discuss the acquisition of anomalous correspondence from the point of view of the psychology of learning. A very simple and fundamental kind of learning is called operant (Skinner 1968), instrumental conditioning (Kimble 1966) or stimulus response learning (Gagné 1970). The most important condition for this is the presence of reinforcement which in the case of anomalous correspondence is the avoidance of confusion and diplopia. This reinforcement will occur immediately when the anomalous correspondence is established. It is well known that such contiguity between response and reinforcement greatly increases learning efficiency. Learning is a gradual process; repetition is neces-

It is of interest to know if the anomalous correspondence is reciprocal that is if the same pairs of retinal points are corresponding whichever eye is fixing. This is illustrated by Fig. 2. For each point in the retina of the fixing eye the position of the corresponding point in the retina of the squinting eye has been calculated from the angle of anomaly. Each position is given as the angular distance from the fovea. The horizontal axes give the positions in the fixing eye and the vertical axes those in the squinting eye. In this way each pair of corresponding points in the retinæ is represented by one point in the diagram.

This way of plotting could be used as well for normal as for anomalous correspondence. The Vieth-Müller circle will in such a diagram be represented by a straight line with the equation $y = x$. A case of anomalous correspondence where the angle of anomaly (a) is constant all over the binocular field will give the line $y = x + a$. (Such a line with $a = -6.1$ is drawn in Fig. 2). If, as in this case, is variable there will be a line with a different slope or a non linear regression. In Fig. 2 the observations with the right eye fixing are marked with circles, those with the left eye fixing with crosses. In two points the circle and the cross do nearly coincide and in those two points the correspondence is reciprocal. In two points the distance between the circle and the cross is more than 1° and the correspondence is probably non reciprocal.

Discussion

It seems now to be generally accepted that anomalous correspondence is in principle harmonious (Bagolini 1961, Hugonnier 1969, p. 196, Parks 1971, p. 115-117). Lack of harmony in anomalous correspondence is secondary, caused by operative or spontaneous change of the angle of squint or dissociation brought about by the arrangements used for the examination.

Normal correspondence is stable and constant, anomalous correspondence is always variable (Tschermak 1899, Bielschowsky 1900, Schlodtman 1900, Adam 1906). This might be an adaptation as the angle of squint is variable and there is a covariation between the angle of squint and the angle of anomaly (Halldén 1952).

Normal correspondence is exact. This is a prerequisite of the high stereoscopic acuity which is comparable to the vernier acuity (Stigmar 1970). Anomalous correspondence is approximate, the subjective angle usually differing a little from zero and it is supplemented by suppression.

Normal correspondence is reciprocal. Anomalous correspondence is sometimes reciprocal, sometimes not.

With normal correspondence fusional movements can be elicited regularly and reproducibly. Fusional movements do occur with anomalous correspondence (Halldén 1952) but not regularly and there is no steady relationship between the fusional stimulus and resulting movement.

With normal correspondence temporary cooperation of horizontally disparate elements within Panum's areas provide stereopsis. This sensory fusion (Werner 1949) might be comparable to the fusional changes of the angle of anomaly which can be provoked by prisms (Halldén 1959) or sometimes occur after surgical correction of strabismus.

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sary to achieve that progressive discrimination of stimulus and differentiation of response which is called shaping. Shaping will explain the covariation between the angle of squint and the angle of anomaly and the other fusional phenomena. The learner of anomalous correspondence is usually a very young child with great flexibility of the sensory apparatus: there is immediate reinforcement and there is continuous repetition during the maybe several years from the onset of the strabismus until treatment is started. Thus the learning of anomalous correspondence occurs in optimal learning conditions and it is not surprising that the retention is very stable and that anomalous correspondence often remains as a permanent obstacle to the attainment of the goal of normal binocular visual function.

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AN ANGIOGRAPHIC AND HISTOLOGIC STUDY OF THE VASCULATURE OF CHOROIDAL MALIGNANT MELANOMA

BY

L. YANKO

Ten cases of malignant melanoma of the choroid examined by fluorescein angiography and routine histologic methods are reported and correlation between the angiographic and microscopic findings is attempted. It is suggested that the fluorescent angiographic appearances in malignant melanoma are better understood in terms of the basic vascular patterns of the tumor as revealed by histology. In assessing the earliest patterns revealed by fluorescein angiography, the initial presence of a loose vascular network and the later appearance of fluorescent dots are readily understood if the histologic arrangement of the tumor vessels is borne in mind.

The presence of wallless tumor blood channels and secondary changes such as hyaline degeneration of the vessel wall and tumoral cells are probably responsible for the late angiographic patterns and the residual fluorescence found in these tumors.

The pigment content of the tumor, hemorrhages within the tumor, the presence of subretinal fluid and vascular damage of the overlying retina are further variables which must be considered when interpreting the pattern of fluorescein angiography in this pathological condition.

Key words: angiography - tumors - melanoma

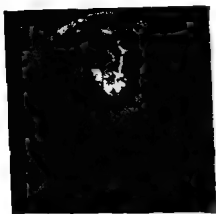


Fig 1

Early arterial phase showing a faint vascular network within the tumoral area



Fig 2

Pre arterial phase showing the presence of a vascular network in the tumoral area

With the introduction of fluorescein angiography and its application to the study of fundal lesions it was hoped that this method might be of value in the differential diagnosis of intraocular neoplasms. Since fluorescein angioscopy of the fundus was first described by Maclean & Maumenee (1960) several attempts have been made to determine the value of fluorescein angiography in the diagnosis of choroidal malignant melanoma (Norton et al 1964) Rubinstein 1967 Snyder Allen & Fraizer 1967 Gitter et al 1968 Oosterhuis & van Waveren 1968 Edwards Layden & Macdonald 1969 Pettit et al 1970).

This malignant tumor shows positive fluorescent staining but no characteristic staining pattern has been observed. Other fundal lesions including choroidal hemangiomas, metastatic tumors, macular degeneration and inflammatory lesions also exhibit fluorescence. The difficulties in differential diagnosis are obvious for the presence of abnormal staining is not specific diagnostically. Thus the vascular system of a malignant tumor requires particular attention and to study the passage of dye in the early phases of its transit through the blood channels may help indicate the tumor's vascular architecture and thus directly facilitate the differential diagnosis of these tumors.

The present study describes and compares the vascular findings in 10 consecutive cases of malignant melanoma of the choroid examined by fluorescein angiography and routine histological methods.



Fig 3

Fig 1 exposed 4 seconds later There is an increased intensity of staining and an extension of the initial tumoral vascular network with parallel filling of the retinal arteries



Fig 4

Fig 2 exposed in the arterial phase showing an increased intensity of staining and extension of the tumoral vascular network



Fig

Dot like fluorescing elements in the vascular phase

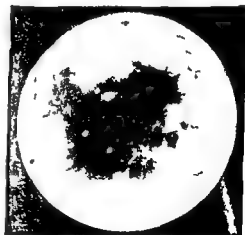


Fig 6

Dot like fluorescing elements



Fig 7

There is a delicately granular staining in the venous phase



Fig 8

Large dark islands within the fluorescing tumoral area and capillary dilatation in the overlying retina

Material and Methods

Ten patients with ophthalmoscopically visible intraocular masses were studied. Following color photography of the fundus a rapid sequence fluorescein angiography (Zeiss equipment) was performed in each case. An Ilford Bright Spectrum blue No 677 gelatin filter was used as an excitation filter and the Kodak Wratten 15 yellow filter was used as a barrier. The film was Kodak Plus X. Five ml of a 10% solution of fluorescein sodium was injected rapidly into the antecubital vein and the frames were taken at intervals of 1.5-2 seconds during the first 30-40 seconds following the injection of the dye and then less frequently. Serial fluorescein photography was continued for at least an hour and occasionally for up to two hours.

All 10 tumors were diagnosed as suspected malignant melanomas of the choroid and the eyes were enucleated. Following fixation in 4% formalin the globes were divided sagittally through the tumors. The gross specimens were examined with a stereomicroscope and microscopic features were described. After embedding in paraffin each tumor was sectioned. In order to preserve the true anatomical relationships of the tumoral vascular channels as they had been recorded by transit fluorescein angiography half of the specimen was cut into tangential sections while the remaining portion was divided into sagittal sections. Serial histological sections were stained with hematoxylin-eosin-periodic acid-Schiff (PAS) and Gomori trichrome and then examined with a light microscope. These serial histological sections and the color fundal photographs were compared with the fluorescein angiography particularly the early transit stages.



Fig 9

Fig 9 exposed in the venous phase and showing leakage of fluorescein from the retinal capillaries

Results

Fluorescein angiography

In 9 of the 10 cases a faint loose vascular network was visible within the tumoral area in the early arterial phase of retinal dye transit and even before the onset of this phase (Figs 1-2) The nearest exposure showed increased staining intensity and an extension of the vascular network as well as filling of the retinal arteries (Figs 3-4) The following photographs revealed extension of the staining beyond the tumoral vasculature and corresponding to the shape and size of the lesion as ascertained ophthalmoscopically and by color photography

In eight of the cases a bright punctate fluorescence distributed all over the tumor but more marked at the periphery was observed during the arteriovenous phase reaching maximum intensity in the venous phase Two types of punctate fluorescence were observed one showed an intensely staining core spreading a faint veil of fluorescein and the other type had distinct clearly defined borders and showed no tendency for enlargement (Figs 5 and 6) These fluorescing dots began to fade during the late venous phase but in three of the cases they were still visible after an hour

Different patterns of fluorescence were observed during the late phases varying from a distinct delicately granulated appearance consisting of alternately bright and dark densely packed irregular small dots (Fig 7) to a more smooth appearance consisting of confluent and larger dark islands within the

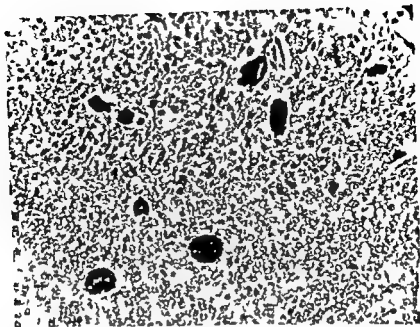


Fig 10

Tangential section of a malignant melanoma of the choroid showing cross sectioned blood channels (Gomori trichrome $\times 260$)

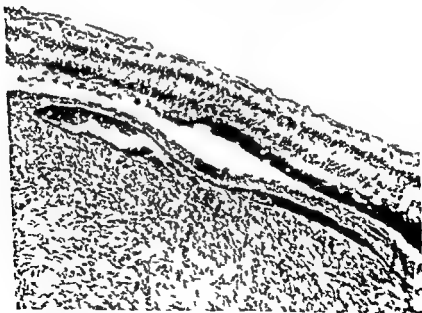


Fig 11

Longitudinal sectioned vessel in the central cortical area of a tumor (Gomori trichrome $\times 100$)



Fig 9

Fig 8 exposed in the venous phase and showing leakage of fluorescein from the retinal capillaries

Results

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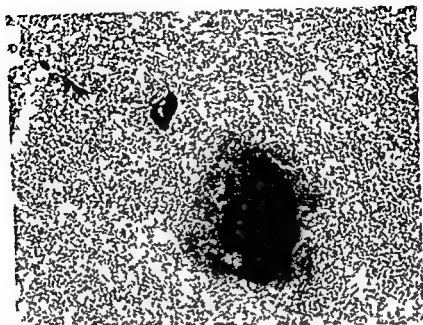


Fig 14

Section of a malignant melanoma of the choroid. Note the degenerative changes in the vessel wall and surrounding tumor cells (Gomori trichrome $\times 100$)

fluorescing tumor mass (Fig 8). In two of the cases a late fluorescent veil obscured the tumor masking its initial staining pattern and extended beyond its borders.

Three of the cases showed extensive capillary alterations in the overlying retina with large areas showing capillary dilatation (Fig 8) and leakage (Fig 9) which were clearly visible overlying the contrasting dark non fluorescent islands within the tumor.

Histology

Stercomicroscopic examination of tumor sections showed a localized elevated mass sometimes mushroom shaped and in all cases protruding toward the vitreous cavity. Varying degrees of serous detachment of the overlying or surrounding retina were found in most of the cases.

The histology of the tumors confirmed the clinical diagnosis of malignant melanoma of the choroid. The tumors consisted mainly of spindle or epitheloid cells or combinations thereof.

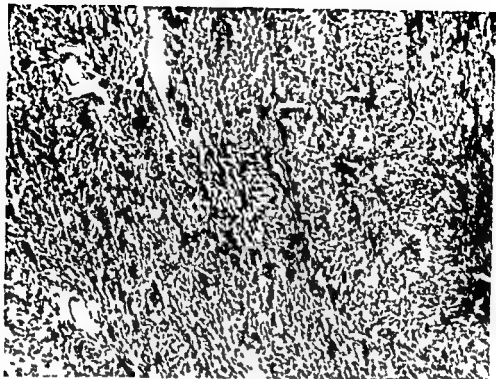


Fig 12

Sagittal section of a tumor showing longitudinally sectioned vessels at the periphery (Hematoxylin and eosin $\times 105$)

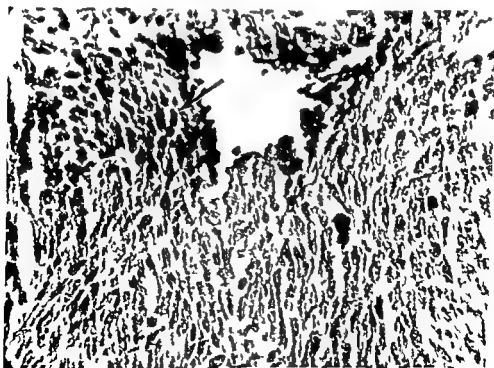


Fig 13

Section of a malignant melanoma of the choroid showing a wall less blood channel and red blood corpuscles (arrow) among the neoplastic cells (Gomori trichrome $\times 470$)

Discussion

The pattern of fluorescence of a tumor in the earliest phases of angiography seems to be related to the number of vascular channels and their architectural arrangement within the tumor. However, the pattern of staining is less characteristic in the later phases of angiography because vascular inefficiency allows fluorescein to leak out into the extravascular spaces.

The faint vascular network observed in the early arterial phase in nine of the cases was of a pattern foreign to the choroid or the retina and possibly reflects the cortical nutritive channels of the tumor. The histological equivalent of this fluorescein pattern is probably represented by the longitudinally sectioned vessels observed in the tangential sections. According to Reese (1963) the head of a malignant melanoma of the choroid contains more vascular spaces than other parts of the tumor, and Terry & Johns (1935) suggested that their presence in the head of the tumor facilitates tumor growth by increasing blood supply.

Previous reports have described early fluorescence in malignant melanomas (Norton et al 1964, 1965; Hill 1966; Snyder et al 1967; Oosterhuis & van Waeren 1968) and in some cases a well defined nutritive vascular system was observed (Charamis, Katsourakis & Mandras 1966; Wessing 1968). According to Behrendt (1967) during the filling phase the fluorescein reaches the arteries through a central core of fluorescein stained blood surrounded by an unstained layer. The central core expands till it eventually covers the whole section. As the tumoral blood channels often are without walls or are permeable due to other reasons, it is easy to understand why a defined vascular system is more easy to visualize in the earliest stages of angiography before the fluorescein has reached the vascular wall and leaked into the extravascular spaces. In eight of the cases a bright punctate pattern of fluorescence was found which was more marked at the periphery of the tumor. This pattern has been described by others (Hill 1968; Rosen 1969) and was a frequent finding in our series, but the literature has no data which describe the histological equivalent of these fluorescing elements.

When the tangential sections were examined the main feature observed was the presence of cross sectioned blood channels which were more numerous at the periphery of the lesion and are assumed to represent vessels with a course perpendicular to the surface of the tumor. After considering the histological findings it would appear that the pattern of punctate fluorescence is due to a cross sectioned view of the fluorescein as it passes through the tumoral blood channels in a posterior-anterior direction. If one accepts the fact that the central core of fluoresceinated blood must reach the anterior end of each vessel



Fig 13

Section of a malignant melanoma of the choroid showing a large area of necrosis surrounded by hemorrhage and inflammation reaction (Gomori trichrome $\times 40$)

Serial tangential sections of the tumors revealed cross sectioned blood channels of different diameters which were more obvious toward the periphery of the tumor (Fig 10) Longitudinal sectioned vessels often were visible in the central cortical area of the tumor (Fig 11)

Serial sagittal sections revealed the reverse findings There was a relatively small number of cross sectioned vessels toward the periphery of the tumor but the number of longitudinal sectioned vessels was greater (Fig 12)

The blood channels were lined either by endothelial cells lying on a basement membrane or by neoplastic cells without any basal membrane (Fig 13) The absence of endothelium and basal membrane allows blood to leak through this canalicular network and circulate freely between the neoplastic cells Hyaline degeneration of tumor cells and vessel walls was found in some sections (Fig 14)

In a few cases large areas of necrosis of the central part of the tumor were associated with areas of hemorrhage and inflammation producing obvious demarcation between necrotic and viable tumor tissue (Fig 15)

Discussion

The pattern of fluorescence of a tumor in the earliest phases of angiography seems to be related to the number of vascular channels and their architectural arrangement within the tumor. However, the pattern of staining is less characteristic in the later phases of angiography because vascular inefficiency allows fluorescein to leak out into the extravascular spaces.

The faint vascular network observed in the early arterial phase in nine of the cases was of a pattern foreign to the choroid or the retina and possibly reflects the cortical nutritive channels of the tumor. The histological equivalent of this fluorescein pattern is probably represented by the longitudinally sectioned vessels observed in the tangential sections. According to Reese (1963) the head of a malignant melanoma of the choroid contains more vascular spaces than other parts of the tumor and Terry & Johns (1935) suggested that their presence in the head of the tumor facilitates tumor growth by increasing blood supply.

Previous reports have described early fluorescence in malignant melanomas (Norton et al 1964, 1965; Hill 1966; Snyder et al 1967; Oosterhuis & van Wa veren 1968) and in some cases a well defined nutritive vascular system was observed (Charamis, Katsourakis & Mandras 1966; Wessing 1968). According to Behrendt (1967) during the filling phase the fluorescein reaches the arteries through a central core of fluorescein stained blood surrounded by an unstained layer. The central core expands till it eventually covers the whole section. As the tumoral blood channels often are without walls or are permeable due to other reasons it is easy to understand why a defined vascular system is more easy to visualize in the earliest stages of angiography before the fluorescein has reached the vascular wall and leaked into the extravascular spaces. In eight of the cases a bright punctate pattern of fluorescence was found which was more marked at the periphery of the tumor. This pattern has been described by others (Hill 1968; Rosen 1969) and was a frequent finding in our series but the literature has no data which describe the histological equivalent of these fluorescing elements.

When the tangential sections were examined the main feature observed was the presence of cross sectioned blood channels which were more numerous at the periphery of the lesion and are assumed to represent vessels with a course perpendicular to the surface of the tumor. After considering the histological findings it would appear that the pattern of punctate fluorescence is due to a cross sectioned view of the fluorescein as it passes through the tumoral blood channels in a posterior anterior direction. If one accepts the fact that the central core of fluoresceinated blood must reach the anterior end of each vessel

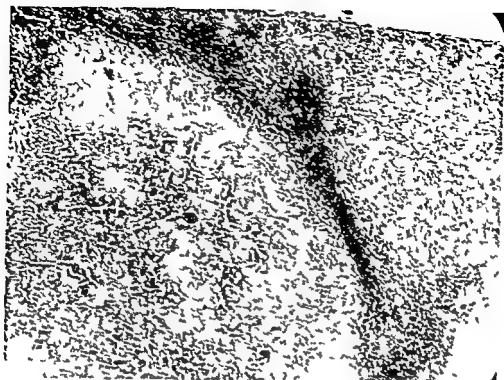


Fig 13

Section of a malignant melanoma of the choroid showing a large area of necrosis surrounded by hemorrhage and inflammation reaction (Gomori trichrome $\times 42$)

Serial tangential sections of the tumors revealed cross sectioned blood channels of different diameters which were more obvious toward the periphery of the tumor (Fig 10) Longitudinal sectioned vessels often were visible in the central cortical area of the tumor (Fig 11)

Serial sagittal sections revealed the reverse findings There was a relatively small number of cross sectioned vessels toward the periphery of the tumor but the number of longitudinal sectioned vessels was greater (Fig 12)

The blood channels were lined either by endothelial cells lying on a basement membrane or by neoplastic cells without any basal membrane (Fig 13) The absence of endothelium and basal membrane allows blood to leak through this canalicular network and circulate freely between the neoplastic cells Hyaline degeneration of tumor cells and vessel walls was found in some sections (Fig 14)

In a few cases large areas of necrosis of the central part of the tumor were associated with areas of hemorrhage and inflammation producing obvious demarcation between necrotic and viable tumor tissue (Fig 15)

this point (Fig 8) Following this initial curtain effect the damaged vessels of the overlying retina provide their own pattern of fluorescence changing the characteristics of the angiogram in the late phases (Fig 9)

Acknowledgment

We thank Mr Moshe Ivry head of the Hadassah Eye Photography Department for the excellent fluorescein angiography

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and then expand to cover its whole diameter before a fluorescein equivalent may be recorded then the appearance of fluorescein at the arterio venous or venous phase is more readily understood. However the relation of the two varieties of punctate fluorescence to defects in the retinal pigment epithelium cannot be entirely overlooked.

Further support for a correlation between morphologic vascular patterns and fluorescein angiographic findings in malignant melanoma of the choroid are given by the observations of François (1963) who using a micro radiographic technique after thorotrast injection showed that the tumor grows concentrically around a central nucleus with the cortical region of the tumor being the most richly vascularized.

In the later stages of angiography these tumors showed various fluorescent patterns already described as granular mottled or patchy. These variable patterns seemed to be based primarily on the presence of vascular channels without walls within the tumor. A canalicular network devoid of endothelium has been described in malignant melanomas and it has been suggested that this represents a potential route for the dissemination of tumor cells into the blood stream (François 1963, Jensen 1964). Similar wall less channels are present in extensions of the tumors described in this study and it is reasonable to assume that each such structure enables the fluoresceinated blood to circulate freely amongst the neoplastic cells.

According to Oosterhuis (1968) changes in the vessel walls of malignant melanomas may result in leakage of dye into the tumor mass which would explain the bright fluorescence found in the late phase photographs. Similar changes were present in some of the tumors described here i.e. hyaline degeneration of the vessel walls and necrotic changes in the surrounding tumoral cells (Fig. 14). These secondary changes within the vessel wall may represent foci of increased leakage as a result of incomplete barrier function at the vascular level. Following the initial leakage there is a selective uptake of dye by the altered vascular and tumoral tissues and this may represent the histological equivalent of the residual fluorescein found after two hours in some tumors reported here. According to Zahl & Waters (1941) the staining of experimental animal tumors is caused by a localized increase of permeability and storage of dye in the stroma of the connective tissue rather than in the tumor cells. Shapiro & Landing (1948) also described intensive fluorescence in necrotic tissues.

The property of light absorption by fundal pigment and its fluorescence barrier effect have already been described (Pettit et al. 1970). The large dark islands of pigment observed in the cortex of the tumor prevent at that particular area the visualization of fluorescein that passes through the tumor beyond

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EMBOLISM OF THE CENTRAL RETINAL ARTERY SECONDARY TO METASTATIC CARCINOMA

BY

AHTI TARKKANEN LAURI MERENMIES and JUDIT MÄKINEN

A 54 year old man experienced sudden loss of vision of one eye and was admitted four hours later for treatment of typical occlusion of the central retinal artery. The patient died three weeks later and the autopsy revealed bronchial carcinoma of the epidermoid type with metastasis in most visceral organs. Microscopic examination of the eye disclosed the central retinal artery to be patent but with atheromatous changes at the level of the lamina cribrosa. The retina showed evidence of acute ischaemic infarction of the inner retinal layers. Tumour emboli were observed in the retinal arterioles. Trypsin digest preparations were also employed to demonstrate tumour cells in the retinal arterioles.

Key words: bronchogenic carcinoma - central retinal artery - embolism - metastatic carcinoma - obstruction - occlusion

The usual cause of occlusion of the central retinal artery is a slow and progressive obliteration of the lumen completed abruptly by terminal thrombosis (Fisher 1959, Lorentzen 1969). Embolism is relatively rare; its most common origin is the carotid artery. However, atheromatous emboli have been demonstrated in the retinal arteries (Ball 1966, Cogan & Kuwabara 1964, Wolter & Ryan 1972). Furthermore, other types of embolisms have also been observed - like that on the patient with recent myocardial infarction (Zimmerman 1965).

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could be restored while the central retina remained oedematous. This is seen in Fig 1 taken 2 days after admission. V.A. of the right eye was at this stage c.f. $1\frac{1}{2}$ meter. However, within four days after admission the patient developed acute abdominal pain and was transferred to a surgical ward. The spleen was stasis. At the operation metastases were found in visceral organs and the patient died three weeks after the loss of vision in the right eye and admission to the Eye Hospital.

Pathologic anatomy Autopsy revealed a large necrotic tumour in the upper lobe of the left lung, with metastasis in most visceral organs including the spleen and the heart muscle. Microscopic examination showed that the tumour was a bronchial carcinoma of the epidermoid type. The grade of differentiation was low with horn pearls only in places. An interesting feature of the tumour was the intravascular infiltration which was observed in almost all visceral organs. An example is shown in Fig 2 where the tumour is seen to infiltrate into a pulmonary vein.

The right eye was grossly normal. The globe was sectioned in horizontal plane and the 1 mm long section of the optic nerve was studied by serial

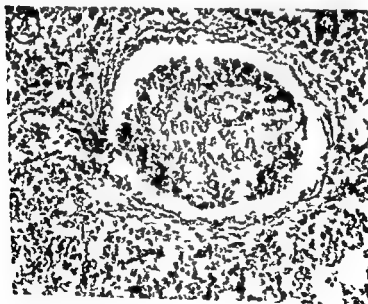


Fig 2

The tumour is seen to infiltrate into the pulmonary vein (haematoxylin-eosin, $\times 200$)

or endocardial myxoma (Manschot 1959) The purpose of the present report is to demonstrate using trypsin digest preparations embolism of the central retinal artery by metastatic carcinoma

Case Description

Clinical history A 54 year old male experienced sudden loss of vision of his right eye and was admitted already four hours later to the Helsinki University Eye Hospital The patient gave a history of previous pulmonary tuberculosis but otherwise his general medical history was not remarkable

Clinical examination The patient appeared to be in good health His blood pressure measured 170/110 mmHg The sedimentation rate was 60 mm/1 hour V A of the right eye was light perception and of the left 10 with correction The tensions measured 17 mmHg o.u. Ophthalmoscopy of the right fundus revealed a milky white central retina with a cherry red spot in the macula The arterioles were severely constricted while the veins were full

Treatment The patient was treated immediately by retrobulbar Priscoline digital massage of the right eye and anticoagulants The retinal blood flow

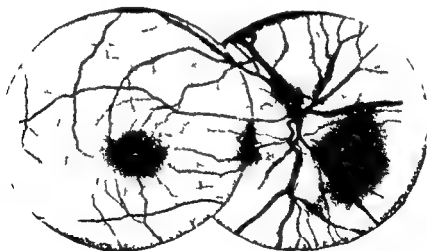


Fig 1

Appearance of the fundus of the right eye on the second day following admission The retina shows oedema the arterioles appear constricted in places while the veins are full

could be restored while the central retina remained oedematous. This is seen in Fig 1 taken 2 days after admission. V A of the right eye was at this stage of $1\frac{1}{2}$ meter. However within four days after admission the patient developed acute abdominal pain and was transferred to a surgical ward. The spleen was atonic. At the operation metastases were found in visceral organs and the patient died three weeks after the loss of vision in the right eye and admission to the Eye Hospital.

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The right eye was grossly normal. The globe was sectioned in horizontal plane and the 17 mm long section of the optic nerve was studied by serial

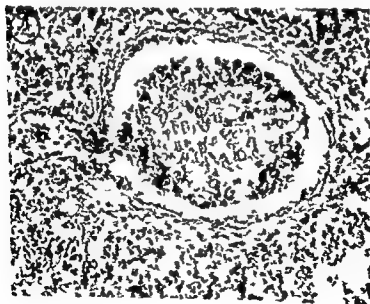


Fig 2

The carcinoma is seen to infiltrate into the pulmonary vein (haematoxylin-eosin, $\times 200$)

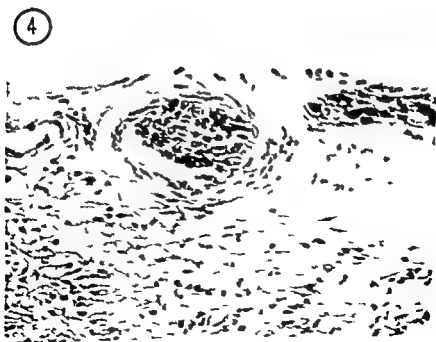
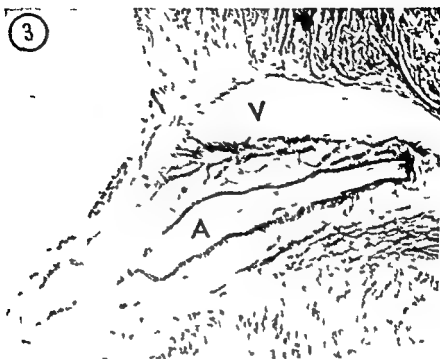




Fig 5

Necrotic tumour embolus in the retinal arteriole. The inner retinal layers appear oedematous (haematoxylin eosin $\times 900$)

sections. The central retinal artery was patent and showed evidence of atherosclerosis at the level of lamina cribrosa (Fig 3). On the other hand the retinal arterioles contained numerous tumour emboli filling the lumen of the vessel (Figs 4, 5 and 6). The choroidal vessels contained also many tumour emboli (Fig 7). Otherwise the retina revealed evidence of acute ischemic infarction of the inner retinal layers with oedema of the inner retina and many destroyed ganglion cells. Trypsin digest preparations showed anaplastic cells in the retinal arterioles (Figs 8 and 9).

Fig 3

The central retinal artery (A) and vein (V) at the level of lamina cribrosa. The lumen of the central retinal artery is patent while there are atheromatous changes in arterial wall (haematoxylin eosin $\times 300$)

Fig 4

Tumour embolus fills the lumen of a retinal arteriole close to the optic disc (haematoxylin eosin $\times 900$)

6



Fig 6

A retinal arteriole is occluded by a tumour embolus while the adjacent venule is patent. The inner retinal layers appear oedematous (haematoxylin eosin $\times 100$)

7



Fig

7 Tumour emboli in the choroidal vessels

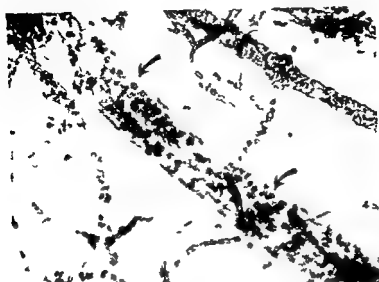


Fig 8

Trypsin digest preparation of the retina showing tumour emboli (arrows)
(haematoxylin eosin $\times 270$)

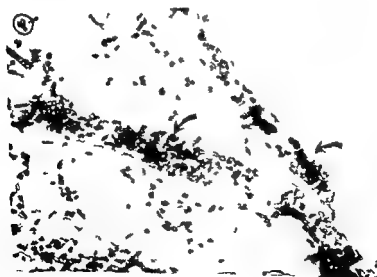


Fig 9

Trypsin digest preparation of the retina Clusters of nucleated cells in the retinal
arterioles (haematoxylin eosin $\times 270$)

6



Fig 6

A retinal arteriole is occluded by a tumour embolus while the adjacent venule is patent
The inner retinal layers appear oedematous (haematoxylin eosin $\times 100$)

7



Fig 7

Tumour emboli in the choroidal vessels

Embolism of the Central Retinal Artery Secondary to Metastatic Carcinoma

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Discussion

Ocular metastasis have been reported as the first clinical manifestation of bronchogenic carcinoma (Crawford & Reese 1969 Gombos & Rakower 1969 Kahn et al 1965) However outside the usual sites choroid ciliary body and iris retinal metastases are rare (Levy & De Venecia 1970) Fewer than 20 cases of retinal metastases by malignant tumours have been described (Font et al 1967) In a careful histological study of 28 eyes with metastasis retinal metastases were found in only 14 % (Block & Gartner 1971)

In his large series of cases with occlusion of the central retinal artery Karjalainen (1971) found atherosclerotic plaques in the retinal arteries The present case is not an exception Atherosclerotic changes were present in the wall of the central retinal artery at the level of lamina cribrosa Occlusion of the central retinal artery occurred probably at this site by the tumour embolus After treatment retinal circulation was restored already after two days following sudden loss of vision (Fig 1) while the embolus moved to retinal arterioles The time for the retinal arterial circulation to re establish itself after occlusion varies (Hayreh 1971) but recanalization had occurred in all cases studied (Karjalainen 1971) The importance of embolism in the aetiology of occlusion of the central retinal artery has been emphasised by Zimmerman (1965) and Wolter & Ryan (1972)

Two cases of tumour embolism in the retinal vessels secondary to primary malignant melanoma of the skin were reported by Font et al (1967) Their statement that such lesions are terminal complications before metastatic death holds true also for the present case At autopsy numerous metastases were found in all visceral organs including the spleen and the heart muscle where metastases are found only infrequently However at the time of loss of vision in the right eye the patient was feeling well and the embolism of the central retinal artery was the presenting sign of the basic illness of the patient

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may persist for years (36 years has been described) The condition occurs thrice as frequently in girls as in boys and has occurred in several members of the same family

Case History

A girl who was 14 months of age when first seen was followed up for three years as an out patient and during numerous readmissions The patient had a diffuse hard thickening and redness of the left upper eyelid The conjunctiva tarsi was covered by a thick meaty diphtheritic membrane When this membrane was removed a bleeding granulating surface remained

In the course of a few days the membrane was reformed and in the course of some weeks it proliferated to such an extent that it projected from the eye A fragment was extirpated and sent to the Ophthalmological Laboratory Rigshospitalet Copenhagen where the following microscopic diagnosis was obtained Exudate and detritus and necrotic conjunctival tissue membrane from conjunctivitis lignosa (sign O A Jensen)

The following treatments were attempted

- 1) Extirpation of the site of the membrane with diathermy and subsequent grafting of a piece of buccal mucosa
- 2) Systematic and local antibiotics
- 3) Argyrol 10 %
- 4) Oculentum Neocortol
- 5) Injections of alpha chymotrypsin

None of these forms of treatment were effective

In October 1971 an epulis was excised from the mandible corresponding to teeth 4 and 5 in the Ear Nose and Throat Department after two unsuccessful attempts at



Fig 1

Thick woody membrane covering the tarsal conjunctiva of the left eye

*Department of Ophthalmology (Head A. Vedel Jensen)
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CONJUNCTIVITIS LIGNEOSA COMBINED WITH A DENTAL AFFECTION

Report of a Case

BY

JENS FRIMODT MØLLER

A case of conjunctivitis lignea which occurred in a girl aged 14 months and which was followed up for three years is described. The characteristic features of the disease are mentioned. It is concluded from the peculiar circumstance of the case having apparently undergone complete regression following a dental extraction that the metabolic disturbance in the mucous connective tissue in the conjunctiva is precipitated by a non-bacterial focus via a possibly autoimmune mechanism.

Key words: conjunctivitis lignea

Conjunctivitis lignea (cl) is a rare subchronic or chronic form of membranous conjunctivitis of unknown etiology. Approximately 65 cases have been described in the literature. As far as can be ascertained, no cases have hitherto been described from Denmark. It is therefore considered to be of interest to publish a case with a characteristic course which was followed up for three years in this Department.

Conjunctivitis lignea is characterized by three pronounced features (Irançois, Hanssens & Victoria-Troncoso 1967): 1) wooden hardness in one or more of the eyelids; 2) formation of pseudomembranes on the conjunctiva, tarsus and 3) occasionally in the late stages membranous overgrowth onto the cornea. The disease commences typically in childhood (age of predilection 2-6 years) and

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Hitherto no infectious etiology has been demonstrated. Cultures have demonstrated mixed infections in numerous cases but these are considered to be secondary as systematic and local antibiotic treatment has had no effect on the recurrent course. The frequent acute onset in association with naso pharyngitis or other systemic disturbances suggests a virus infection. In one case only (Chambers et al 1969) did it prove possible to demonstrate a slowly growing adenovirus and this is therefore not considered to be of causal significance. The question of an autoimmune mechanism has frequently been discussed. In the lesion infiltration with plasma cells and lymphocytes is seen. Seven instances are described in which it developed in more than one member of the same family and transient improvement has been described on treatment with steroids. However the sedimentation rate is rarely raised and it has not proved possible to demonstrate increased quantities of circulating gammaglobulins or cell bound antigens. Other authors (Guerra Tosi & Bonann 1969) consider that c1 and isolated amyloidosis in the conjunctiva are identical from the findings of amyloid substance and a large number of plasma cells in the lesions. These diseases have similar macroscopic appearances and tendencies to recur (Lisch 1972) but decisive histological differences are present.

François et al (1966) have studied in detail the clinical, histopathological, histochemical and therapeutic aspects of c1 and they conclude that the disease is due to a hereditary disturbance in the metabolism of the mucous connective tissue. Histopathologically the actual membrane is found to be fibrinous with degenerated inflammatory cells and hyalinized connective tissue. The conjunctival epithelium is thickened, dyskeratotic and infiltrated with fibrin. The epithelium forms invaginations into the underlying tissue and may form crypts containing fibrin and degenerated cells. The submucous tissue shows a dense exudative inflammation with fibrosis and vascularization. The lesion contains large quantities of mucopolysaccharides composed of hyaluronic acid, chondroitin sulphate A or C.

In some cases of c1, particularly when accompanying systemic manifestations are present, corneal complications with vascularization, keratomalacia, perforation and atrophy of the eye may occur.

Until recently no effective treatment has been available. In addition to the therapeutic measures attempted here, intensive beta irradiation has been administered without effect. On the basis of the histochemical findings, François & Victoria Troncoso (1968) suggested treatment consisting of instilling hyaluronidase possibly combined with alpha chymotrypsin for removal of the pseudomembrane as the first promising therapy (Bietti & Quaranta 1969, Firat & Tınaztepe 1972).

This patient was sent for in April 1972 with the intention of attempting the



Fig 2

The extirpated membrane



Fig 3

Five months after the dental extraction the membrane has disappeared and only a small scar remains

incision and antibiotic therapy by a dentist. Immediately after discharge swelling in the right side of the floor of the mouth reformed. One month later teeth 4 and 5 were extracted by the dentist. Immediately after this the swelling in the floor of the mouth disappeared and the membrane in the conjunctiva gradually diminished in size. On out patient follow up examination in April 1962 slight scarring in the conjunctiva was all that remained and the eyelid felt soft and normal.

Discussion

Borel (1933) gave this condition its present name. Cases of an undetermined nature to which a diphtheritic etiology was ascribed but which probably belonged to this type have been described in the literature since 1869. The condition was not recognized as a clinical entity until after the detailed clinical and pathological studies by Lajo Pavia (1924-36).

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PSEUDOEXFOLIATION OF THE LENS CAPSULE AND LIBERATION OF IRIS PIGMENT

BY

U KRAUSE J HELVE and H FORSIUS

A total of 920 inmates of old people's homes all over 60 years of age were examined for pseudoexfoliation of the lens capsule. The incidence recorded for the age group 60-69 years was 10%, 70-79 years 21.3% and 80-89 years 37.8%. The intraocular tension of the eyes with pseudoexfoliation averaged 17.5 mmHg against an average of 15.4 mmHg in normal eyes. After mydriatics pigmented floaters were seen in the aqueous humour of 61.5% of the normal eyes and 83.3% of the eyes with pseudoexfoliation. In these latter eyes moreover the pigment liberation was distinctly more marked. The trabecular region of the affected eyes was more pigmented than that of the normal eyes. The mechanism by which pseudoexfoliation possibly affects pigment liberation and trabecular pigmentation is discussed.

Key word: pseudoexfoliation - fibrillogluthia epitheliocapsularis - pigmented aqueous floaters - trabecular pigment - frequency - Finland

Lindberg (191) was the first to describe pseudoexfoliation of the lens capsule (hereafter called simply pseudoexfoliation). Figures quoted in the literature concerning its geographical incidence among the normal population range from 0.1% (Egypt) to 48% (Russia) (Maghraby 1931; Hoorgina 1929). Aasved (1969) has reviewed the literature on the occurrence of pseudoexfoliation up to 1969. Among the more recent authors Bartholomew (1970) reports that pseudoexfoliation is by no means uncommon in Southern Bantu and Faulkner (1971) found it in 38% of Navajo Indians aged 60 years or more.

treatment proposed by François. It was a striking observation that the disease had become quiescent following the dental extraction five months previously. This phenomenon has not been described previously. Some cases have however "burnt out" without known reason in the course of varying periods of time. Some of these have recurred after long periods (11 and 25 years).

It must be considered probable that the condition is due to a disturbance in the metabolism of connective tissue. The trigger mechanism which starts the condition however is unknown. The case described here demonstrates the presence of a precipitating focus which is not bacterial. How the metabolic disturbance in the conjunctival connective tissue is initiated is best explained by an autoimmune pathogenesis although this cannot be entirely proved.

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PSEUDOEXFOLIATION OF THE LENS CAPSULE AND LIBERATION OF IRIS PIGMENT

BY

U KRAUSE J HELVE and H FORSIUS

A total of 970 inmates of old people's homes all over 60 years of age were examined for pseudoexfoliation of the lens capsule. The incidence recorded for the age group 60-69 years was 10%, 70-79 years 21.3% and 80-89 years 37.8%. The intraocular tension of the eyes with pseudoexfoliation averaged 11 mmHg against an average of 13.4 mmHg in normal eyes. After mydriatics pigmented floaters were seen in the aqueous humour of 61.5% of the normal eyes and 83.3% of the eyes with pseudoexfoliation. In these latter eyes moreover the pigment liberation was distinctly more marked. The trabecular region of the affected eyes was more pigmented than that of the normal eyes. The mechanism by which pseudoexfoliation possibly affects pigment liberation and trabecular pigmentation is discussed.

Key words: pseudoexfoliation - fibrillogenesis epitheliocapsularis - pigmented aqueous floaters - trabecular pigment - frequency - Finland

Lindberg (1911) was the first to describe pseudoexfoliation of the lens capsule (hereafter called simply pseudoexfoliation). Figures quoted in the literature concerning its geographical incidence among the normal population range from 0.1% (Egypt) to 48% (Russia) (Maghraby 1931; Hoorghina 1979). Aasved (1969) has reviewed the literature on the occurrence of pseudoexfoliation up to 1969. Among the more recent authors Bartholomew (1970) reports that pseudoexfoliation is by no means uncommon in Southern Bantu and Faulkner (1971) found it in 38% of Navajo Indians aged 60 years or more.

Forsius & Luukkka (1972) reported pseudoexfoliation among old Skolt Lapps (aged 70-79 years) in northern Finland quoting an incidence of 50%. On the other hand population studies among the Eskimos in Alaska, Greenland and Canada revealed no cases of pseudoexfoliation.

The wide differences between the incidence figures quoted in the literature may be due to the selection of the material studied e.g. hospital series or general population and the age distribution (Aasved 1969). In a later study Aasved (1971) reports that the incidence of pseudoexfoliation in subjects aged 40-49 years is 0% but in those aged over 50 it is 7.6%. If furthermore the clinical picture of the disease is not adequately known and unless particular attention is given to its existence the incidence figures obtained are erroneous. It has in fact proved necessary to correct earlier incorrect numerical data for several countries (Aasved 1969).

Vogt (1925), Pillat (1934) and Bird (1935) have described how in glaucomatous eyes with pseudoexfoliation mydriasis caused in excessive liberation of pigment floating in the aqueous humour. According to Tarkkanen (1962) the phenomenon can only be noted in eyes with pseudoexfoliation. Mitsui & Takagi (1961) reported that sympathomimetic mydriatics induced pigmented floaters in the aqueous in 4.6% of eyes without any signs of iritis. Kristensen (1965) has said that pigmented floaters are noted in connection with mydriasis in 9% of the eyes without glaucoma or iritis. The older the patients examined the more frequent and the more distinct is the phenomenon (Mitsui & Takagi 1961, Kristensen 1965, Aggarwal & Beveridge 1971). The mydriatic induced pigmented floaters are 10-15 μ m in diameter. A maximum of floaters appears 1-2 hours after mydriasis and they disappear from the aqueous humour in 12-24 hours. The particles are apparently pigment granules from the pigment epithelium cells according to Mitsui & Takagi (1961). Excessive pigment liberation may produce a rise of the intraocular tension in the eyes with open angle glaucoma but the mechanism in this case is different from that in the water provocative test (Kristensen 1965, 1968). The chamber angle may often be heavily pigmented in pseudoexfoliation (Petersen 1958, Tarkkanen 1967, Sugar 1966, Harven & Hutchinson 1967). In unilateral pseudoexfoliation the chamber angle of the affected eye is often more heavily pigmented than that of the fellow eye (Tarkkanen 1962). Mitsui & Takagi (1961) found that in the patient in whom mydriasis produces profuse pigment liberation the degree of trabecular pigmentation is greater than in persons without this liberation.

The purpose of the present work was to study the incidence of pseudoexfoliation among the older age groups in Finland and to analyse the possible correlation of the disease to pigment liberation by mydriasis and to the trabecular pigmentation.

Material and Methods

The series consisted of 220 persons 93 men and 122 women. They were selected at random from the Old People's Homes of the City of Oulu and the surrounding communes. The place of birth of the participants was recorded in order to ascertain whether the series could be characterized as an isolate. The mean age of the series was 75.6 years: men 74.7 and women 76.4 years.

Every eye as far as possible was examined as follows. First the number of pigmented floaters in the aqueous humour was estimated using the classification proposed by Mitsui (1943) (Table I). A Haag Streit 900 slit lamp with 16 fold magnification was used: the slit was 2 mm high and the width screw in position 10 (Kristensen 1968). The intraocular tension was measured with an applanation tonometer and the grade of trabecular pigmentation was evaluated according to the principle of Becker & Schaeffer (1965) with grade 0 corresponding to unpigmented and grade 4 to a very heavily pigmented trabecular meshwork. A mean value of the figures indicating pigmentation at 12, 3, 6 and 9 o'clock was calculated for each eye for further statistical analysis. Signs of pseudoexfoliation were sought in the pupillary margin, lenticular surface and the posterior corneal surface. One to two hours after instillation of mydriatics (Phenylephrine 10% and Tropicamide 1%) the intraocular tension was measured and the number of the pigment floaters present was evaluated using the classification described above. Signs of pseudoexfoliation were again sought using the method described. Only definite findings were recorded as positive.

The scheduled series of examinations could be carried out almost completely on 206 patients.

Table I
Scale of pigmented floaters in the aqueous humour (Mitsui 1943)

Grade	Number of floaters
0	No floaters
1	One or more floaters in the whole aqueous humour One or more floaters within the range of a single beam
2	About ten floaters within the range of a single beam
3	Up to a hundred floaters within the range of a single beam Hundreds of floaters within the range of a single beam
4	Innumerable floaters within the range of a single beam

Forsius & Luukka (1972) reported pseudoexfoliation among old Skolt Lapps (aged 70-79 years) in northern Finland quoting an incidence of 30.7%. On the other hand population studies among the Eskimos in Alaska, Greenland and Canada revealed no cases of pseudoexfoliation.

The wide differences between the incidence figures quoted in the literature may be due to the selection of the material studied, e.g. hospital series or general population, and the age distribution (Aasved 1969). In a later study Aasved (1971) reports that the incidence of pseudoexfoliation in subjects aged 40-49 years is 0% but in those aged over 80 it is 7.6%. If furthermore the clinical picture of the disease is not adequately known and unless particular attention is given to its existence, the incidence figures obtained are erroneous. It has in fact proved necessary to correct earlier incorrect numerical data for several countries (Aasved 1969).

Vogt (1925), Pillat (1934) and Bard (1935) have described how in glaucomatous eyes with pseudoexfoliation mydriasis caused an excessive liberation of pigment floating in the aqueous humour. According to Tarkkanen (1962) the phenomenon can only be noted in eyes with pseudoexfoliation. Mitsui & Takagi (1961) reported that sympathomimetic mydriatics induced pigmented floaters in the aqueous in 4.6% of eyes without any signs of iritis. Kristensen (1963) has said that pigmented floaters are noted in connection with mydriasis in 19% of the eyes without glaucoma or iritis. The older the patients examined the more frequent and the more distinct is the phenomenon (Mitsui & Takagi 1961, Kristensen 1965, Aggarwal & Beveridge 1971). The mydriatic induced pigmented floaters are 1.0-1.5 μ m in diameter. A maximum of floaters appears 1-2 hours after mydriasis and they disappear from the aqueous humour in 12-24 hours. The particles are apparently pigment granules from the pigment epithelium cells according to Mitsui & Takagi (1961). Excessive pigment liberation may produce a rise of the intraocular tension in the eyes with open angle glaucoma but the mechanism in this case is different from that in the water provocative test (Kristensen 1963, 1968). The chamber angle may often be heavily pigmented in pseudoexfoliation (Petersen 1958, Tarkkanen 1962, Sugar 1966, Horven & Hutchinson 1967). In unilateral pseudoexfoliation the chamber angle of the affected eye is often more heavily pigmented than that of the fellow eye (Tarkkanen 1962). Mitsui & Takagi (1961) found that in the patient in whom mydriasis produces profuse pigment liberation the degree of trabecular pigmentation is greater than in persons without this liberation.

The purpose of the present work was to study the incidence of pseudoexfoliation among the older age groups in Finland and to analyse the possible correlation of the disease to pigment liberation by mydriasis and to the trabecular pigmentation.

AGE GROUPS	WITHOUT PSEUDOEXFOL		WITH PSEUDOEXFOL	
	Mean Mitsui value	No. of eyes	Mean Mitsui value	No. of eyes
60-69	2.46	90	4.00	6
70-79	2.43	166	3.96	30
80-89	1.56	78	2.91	24
90-99	0	1	—	—
Total	2.23	335	3.55	60

Fig. 7

Liberation of pigmented floaters into the aqueous humour after mydriatics graded according to Mitsui's scale (1943) in eyes with and without pseudoexfoliation

of mydriatics the intraocular tension in the eyes with pseudoexfoliation was 17.5 mmHg and in those without pseudoexfoliation 15.4 mmHg. This difference in tension is statistically almost significant. The glaucomatous eyes under treatment were excluded from these calculations. Twenty-four subjects had unilateral exfoliation without glaucoma. On the average the tension in the eyes with pseudoexfoliation was 1.4 mmHg higher than in the fellow eye.

The tension change following the instillation of mydriatics averaged +2.1 mmHg (range +17 and -4 mmHg) in eyes with pseudoexfoliation. The corresponding figures for the eyes without pseudoexfoliation were +1.1 mmHg (range +13 and -1 mmHg). Before the instillation of mydriatics a pigmented floater was only occasionally noted in the aqueous humour. The mean initial value according to the Mitsui (1943) classification was therefore almost Grade 0. After mydriatics the pigment liberation could be graded in 395 eyes. Of the eyes with pseudoexfoliation pigment liberation was noted in 83.3% and in these (10) eyes the Mitsui value averaged 3.55. Of the eyes without pseudoexfoliation mydriasis induced a pigment liberation in 63.5% and the mean Mitsui value for the (335) eyes was 2.23. The difference between the Mitsui values was statistically highly significant (Fig. 7). In unilateral pseudoexfoliation also a similar difference was elicited: the mean pigment liberation value in the affected eye was 3.4 and in the fellow eye respectively 2.4. These

Results

The patients places of birth covered a large area of the central part of the country and therefore the population examined had no characteristics of an isolate

The examination after mydriasis revealed 48 patients with pseudoexfoliation. In 18 patients it was bilateral and in 30 unilateral. The total of affected eyes was thus 66. None of the 14 patients to whom no mydriatics could be administered showed any signs of pseudoexfoliation. The incidence of pseudoexfoliation of the lens capsule among the 220 subjects examined was 21.8%. The figure for men was 21.4% and for women 22.1%. Fig. 1 shows the increase in pseudoexfoliation among both men and women in the older age groups. From a mean incidence of 10% among those aged 60-69 it increased to 21.3% among those aged 70-79 and ultimately to 32.5% among patients aged 80-89 years.

The primary diagnosis of pseudoexfoliation was correct for 50 eyes and after mydriasis the disease was discovered in a further 16 eyes. Mydriasis disproved the assumption of pseudoexfoliation in three eyes. In a total of 19 eyes which was 4.6% of the eyes examined an erroneous diagnosis was made before the dilatation of the pupil.

Glaucoma had previously been diagnosed in 30 eyes of 16 patients and 11 of these eyes were affected with glaucoma capsulare. Prior to the instillation

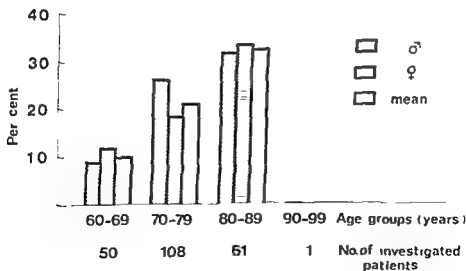


Fig. 1
Incidence of pseudoexfoliation (per cent) in the different age groups

materials from Norway England and Germany are composed of the same age groups as the present series In every age group our incidence figures are higher than those for the said three countries It may be mentioned for comparison that in Norway the age group 80-89 years had an incidence of 7.6% (Aasved 1971) against the respective incidence of 32.8% in Finland Since Aasved's and the present studies describe the incidence of pseudoexfoliation among the inmates of old people's homes the results in our opinion are comparable and they must be interpreted as showing that the incidence of pseudoexfoliation in Finland really is higher than in the countries studied by Aasved A racial difference may be involved here the existence of such a difference is suggested by the studies of isolates by Forsius & Luukka (1973)

Pigmented floaters produced by mydriasis were seen in 61.5% of the examined eyes without pseudoexfoliation We could not substantiate the finding (Tarkkanen 1969) that pigment liberation was to be seen only in eyes with pseudoexfoliation In the affected eyes the incidence amounted to 83.3% and moreover the aqueous humour contained a highly significantly larger number of pigmented floaters than that of the normal eyes

It is known that the iris liberates pigment more frequently the older the subjects are (Mitsui & Takagi 1961 Kristensen 1965 Aggarwal & Beveridge 1971) According to the present results the grade of pigment liberation seems to reach its peak between 60 and 79 years of age after which the number of pigmented floaters would seem to decrease Since the pigment epithelium of the iris is of neuroretinal origin it has no regenerative ability This might explain the present finding

It has often been claimed previously that the trabecular region of the eyes with pseudoexfoliation is more heavily pigmented By statistical methods the observations have now been proved correct Mitsui & Takagi (1961) assumed that the pigmented floaters in the aqueous humour are pigment granules from the pigment epithelium cells of the iris and the application of mydriatics causes a rupturing of degenerated cells It does not seem inconceivable that the mechanism gains in strength when the iris moves along the uneven (Buzacca 1976) surface of an exfoliating lens Pseudoexfoliation in this way would gradually lead to a heavier than normal pigmentation of the trabecular region and also to the observed massive pigment liberation in connection with mydriasis

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	WITHOUT PSEUDOEXFOL		WITH PSEUDOEXFOL	
	No of eyes	GP	No of eyes	GP
♀	178	0.73	27	1.79
♂	156	0.86	27	1.20
♀+♂	334	0.79	54	1.49

Fig. 3

The grade of pigment (GP) in the trabecular region estimated according to Becker & Shaffer (1965) in eyes with and without pseudoexfoliation

figures are based on the results for 24 cases of unilateral pseudoexfoliation. The significance of the difference between the figures has not been statistically analysed.

The present results show, therefore, that the pigment liberation after mydriatics seems to reach its maximum at the age of 60-79 years (Fig. 2) after which the pigmentary dust is less intense. This is true both of the eyes with and without pseudoexfoliation.

The grade of pigmentation of the chamber angle in the normal eyes averaged 0.79 and in the eyes with pseudoexfoliation 1.49. The difference between these figures is statistically significant (Fig. 3). No similar difference was noted in the cases with unilateral exfoliation.

Discussion

As far as Finland is concerned, the incidence of pseudoexfoliation is known only for two isolates (Forsius & Eriksson 1961; Forsius & Luukka 1973). The present study was an attempt to investigate the incidence of pseudoexfoliation in an unselected normal population, if it is assumed that this can be represented by the inmates of old people's homes.

The series examined, as a result, contains no age groups under 60. The findings reported are not comparable with the incidence figure of 8.6% quoted by Forsius & Eriksson (1961), which shows the occurrence of the disease among subjects aged over 40 without any detailed age classification. Arveds (1969)

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CEROID LIPOFUSCINOSIS (BATTEN'S DISEASE)

First ophthalmological report of cytoplasmic inclusions
in the Schwann's cell of the sural nerve in two patients with an
amaurotic familial idiocy

BY

J M BOLMERS F J M GABREELS E M G JOOSTEN and
A GABREELS FESTEN

Two patients with the clinical picture of a late infantile and juvenile amaurotic familial idiocy (Batten's disease) have been examined electron microscopically. The typical cytoplasmic inclusion bodies in the Schwann cells of the sural nerve supported this clinical diagnosis. The importance of sural nerve biopsy in patients with a cerebroretinal degeneration is discussed.

Key words: tapetoretinal degeneration - cerebroretinal degeneration - late infantile amaurotic familial idiocy - juvenile amaurotic familial idiocy - Batten's disease - sural nerve biopsy - retinitis pigmentosa - central nervous system disease

Recent biochemical and morphological investigations have shown that the term amaurotic familial idiocy (AFI) comprises a heterogeneous group of diseases (Zeman & Dyken 1969) which can be separated more or less into two main groups:

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Recent biochemical and morphological investigations have shown that the term amaurotic familial idiocy (AFI) comprises a heterogeneous group of diseases (Zeman & Dyken 1969) which can be separated more or less into two main groups:

1 Gangliosidoses Gangliosidoses are diseases in which gangliosides accumulate in brain and/or visceral organs due to a disorder in the breakdown of these substances as a result of an enzyme deficiency.

In the wider sense the gangliosidoses are included in the so called lysosomal thesauridoses and in the more narrow sense, in the so called sphingo glycolipidoses.

2 Ceroid lipofuscinosis (Batten's disease) Zeman & Dyken (1969) introduced the name ceroid lipofuscinosis for a group of diseases which comprise a number of cases from the group of the late infantile ALI (Jansky Bielschowsky) the juvenile ALI (Batten Spielmeier-Vogt) and the adult ALI (Kufs-Haller-vorden). Various authors though (among others Zeman & Dyken 1969) have been able to demonstrate by careful clinical and pathological anatomical investigation that this group of diseases constitutes a discrete entity and must be dissociated from gangliosidoses proper.

Gonatas et al (1968) Elfenbein et al (1969) and Carpenter et al (1972) attempted to distinguish the late infantile and juvenile forms on the basis of electron microscopic findings. The late infantile form was characterized by an accumulation in neurons and astrocytes of cytosomes with curvilinear profiles whereas in the juvenile form the main finding was an accumulation of cytosomes with fingerprint profiles and cytosomes with rectilinear profiles. Moreover there were transitions morphologically.

In the past few years it has been found that the above mentioned ultrastructural disorders also are demonstrable in tissues outside the central nervous system namely in the neurons and smooth muscle of the rectum and appendix (Duffy et al 1968; Elsner et al 1969; Carpenter 1972; van Haest 1972) in the spleen (Duffy et al 1968) in eccrine sweat glands of the skin in skeletal muscles in Schwann's cells of a peripheral nerve (Carpenter et al 1972) and in lymphocytes (Witzleber 1971).

For the prognosis and for genetic counseling it is important to make a diagnosis as early as possible. Nowadays one is able to arrive at the diagnosis via histological and enzyme histochemical examination of biopsy material which is simple to obtain (skin, skeletal muscle and peripheral nerve) and to make a diagnosis with rather good reliability via ultrastructural examination. The examination of lymphocytes is not specific enough because the ultrastructural disorders are also found in Niemann Pick disease (Witzleber et al 1971).

In this article this will be illustrated with the help of sural nerve biopsies of two patients: one suffering from the late infantile form and the other from the juvenile form.

Case Reports

CASE I

Late infantile form

BA a boy born 2-10-1965 to healthy parents. In the family consanguinity has occurred. MMM and PMM are sisters. There is no blindness or neurological disease in the family. Pregnancy and partus were undisturbed. Until the age of 3 years the patient developed normally. After this age a clear kink in development appeared expressing itself in generalized epileptic manifestations, visual disturbances and regression of physical functions.

At the age of 5 years he was hospitalized for observation in the child neurology department because of marked deterioration.

Neurological examination revealed a double-sided pyramidal cerebellar syndrome. *Ophthalmological findings:* Good fixation, possibility following movements seem intact. Visual acuity not able to be determined. Fundus oculi: the vessels are normal, the optic disk shows a waxy pale temporal half. The fovea reflex is absent, the macula reflex is partially discontinued, the fovea lies in a reddened surround with a coarse grained pigmentation around this up to the edge of the macula, with an area of depigmentation in between. The corpus vitreum is clear and the lens shows no abnormalities. ERG is extinguished.

CASE II

Juvenile form

FA a girl born 2-1-1965 to healthy parents. There is no consanguinity. There is no blindness or neurological disease in the family. Pregnancy and partus were undisturbed. The psychomotor development was normal. After 5 years of age a kink in development appeared showing primarily as a deterioration in mental functions as well as a progressive visual deterioration.

On neurological examination no abnormalities were found.

Ophthalmological findings: The eye movements are undisturbed, the visual acuity is right 1/10 and left 1/10, the lens has an even opacity increase, the corpus vitreum shows a clouded aspect but without cells, the fundus oculi showed A V = 1/3. The optic disk showed a transparent pale aspect but without a clear atrophy, the fovea and macula reflex were both discontinued. The pigmentation of the posterior pole had a coarse grained aspect with a distinct condensation around the macula and throughout the fovea which lies right as it were in a pigmented pit. The pigmentation of the periphery showed an identical aspect with depigmentations in between. The posterior pole has a star shaped reflex which appears to be caused by a folding or condensation of the membrana limitans interna (Figs 1-2).

The EKG is extinguished. The fundus picture 3 months later revealed a distinct increase in the existing pigmentation in the retina.

Laboratory investigation: Cases I and II (Cerebral blood and urine examination showed no abnormalities. Liver and kidney functions were normal. Protein spectrum and immuno electrophoresis pattern were normal).

(1-1-1967) Iodine tracer examination, thyroid gland scintigraphy, GTT



Fig 1

Posterior pole of the right eye of case II. A distinct condensation of coarse grained pigment around the macula and the fovea which lies as it were in a pigmented pit

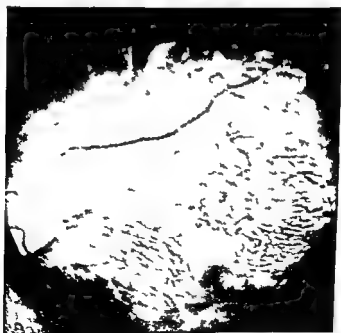


Fig 2

Posterior pole of the left eye of case II. A condensation of coarse grained pigment around the macula and the fovea

cortisol rhythm and metapiron test were normal. Reactions for lues and toxoplasmosis were negative. Amino acid spectrum in urine was normal. Total lipids, cholesterol, triglycerides α and β lipoprotein percentages and phospholipid spectrum of the erythrocytes and plasma gave normal values. Excretion of acid mucopolysaccharide in the urine was normal as was phytanic acid in serum. Lysosomal enzymes in leukocytes: arylsulfatase A, hexosaminidase A and B, β galactosidase, α fucosidase, mannosidase and acid phosphatase were normal.

Bone marrow puncture normal. No vacuolization in lymphocytes. Liquor (cells, protein, protein spectrum, immuno electrophoresis, LDH, GOT, GPT) normal.

EEG: case I showed a generalized petit mal variant epilepsy; case II showed centrencephal dysregulations.

EEFC: moderate diffuse widening of the ventricle system.

EMG: no deviations.

Conductive velocity of peripheral nerve (including n. peroneus) was normal.

Sural nerve biopsy

Methods for the morphological examination: Material for histological examination was fixed in 10% formalin, embedded in paraffin and stained by the following methods:

hematoxylin-eosin, periodic acid-Schiff (PAS), luxol fast blue, cresylfast violet (Kluver-Barrera), Wallart-Mallory-Azan, toluidine blue 1/600, pH 4.5 and pH 5.5, and a silver impregnation according to Bodian. Frozen sections were stained with Sudan III, Sudan black B and cresylfast violet according to Hirsch & Leiffer (1954).

In cryostat sections activity of the following enzymes was demonstrated: lactate dehydrogenase, malate dehydrogenase, succinate dehydrogenase (Pearse 1960), NADH-tetrazolium oxidoreductase (Novikoff et al. 1961), glucose 6-phosphate dehydrogenase (Scarpelli et al. 1959), thiamine pyrophosphatase (Jongkind et al. 1961), adenosinetriphosphatase (Pearse 1960) and acid phosphatase (Barka & Anderson 1962). A fasciculus of the sural nerve was reserved for the teased fiber preparation according to the method of van Dyck & Löffgren.

Specimens for electron microscopy were fixed in buffered glutaraldehyde 3% buffered with sodium cacodylate buffer, pH 7.4 at 4°C for three hours, postfixed with 1% OsO_4 in Palade buffer, pH 7.4, dehydrated in a graded series of alcohol and embedded in epon. Ultra thin sections were stained with combinations of uranyl acetate and lead citrate and examined with a Philips EM 300 electron microscope.



Fig 1

Posterior pole of the right eye of case II. A distinct condensation of coarse grained pigment around the macula and the fovea which lies as it were in a pigmented pit



Fig 2

Posterior pole of the left eye of case II. A condensation of coarse grained pigment around the macula and the fovea

cortisol rhythm and metapiron test were normal. Reactions for lues and toxoplasmosis were negative. Amino acid spectrum in urine was normal. Total lipids, cholesterol, triglycerides α and β lipoprotein percentages and phospholipid spectrum of the erythrocytes and plasma gave normal values. Excretion of acid mucopolysaccharide in the urine was normal as was phytanic acid in serum. Lysosomal enzymes in leukocytes: arylsulfatase A, hexosaminidase A and β galactosidase, α fucosidase, mannosidase and acid phosphatase were normal.

Bone marrow puncture normal. No vacuolization in lymphocytes. Liquor (cells, protein, protein spectrum, immuno electrophoresis, LDH, GOT, GPT) normal.

EEG: case I showed a generalized petit mal variant epilepsy; case II showed centrencephal dysregulations.

LPEG: moderate diffuse widening of the ventricle system.

ENG: no deviations.

Conductive velocity of peripheral nerve (including n. peroneus) was normal.

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Results

In case I no histologically or enzyme histochemically remarkable details were found. In 25 teased fibers with a total of 114 segments no signs of demyelination were seen. With the electron microscope we found membrane bound cytosomes mostly with the typical curvilinear aspect (Duffy et al 1968) and generally in Schwann cells associated with unmyelinated fibers (Fig 3).

In some smooth muscle cells of one vessel in the epineurium we also observed some curvilinear bodies. Case II using histological techniques was shown to have a normal sural nerve. Enzyme histochemically however an increased perinuclear activity of acid phosphatase was shown in many of the Schwann cells while in some cells this activity also appeared to extend outside the normal perinuclear localization.

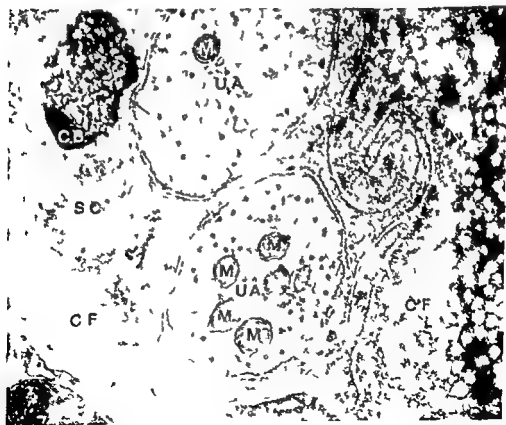


Fig 3

Enclosed in the cytoplasm of a Schwann cell belonging to an unmyelinated fiber there is a curvilinear body (→) (41 000). CB = curvilinear body CF = collagen fiber M = myelinated axon MA = mitochondria UA = unmyelinated axon N = nucleus of a Schwann cell



Fig 4

Enclosed in the cytoplasm of a Schwann cell is a membrane bound cytosome with fingerprint material (→) ($\times 19,500$) For abbreviations see Fig 5

In 29 teased fibers (total 125 segments) 2 widened nodes of Ranvier were seen in one fiber as well as an intercalated segment

Electron microscopy demonstrated cytosomes in the cytoplasm of Schwann cells associated with myelinated and unmyelinated axons sometimes bound with a membrane and within it 5-10 stacks of fingerprint (Donahue et al 196) material occasionally accompanied by some glycogen like granules (Fig 4-5) Sometimes there were some opaque droplets visible like those frequently associated with lipofuscin granules The fine structure corresponded with the report of Suzuki et al (1965) in that the fingerprint material disclosed periodicity of about 90 Angstrom and that each lamellar structure was composed of two dense lines separated by a narrow electron translucent line

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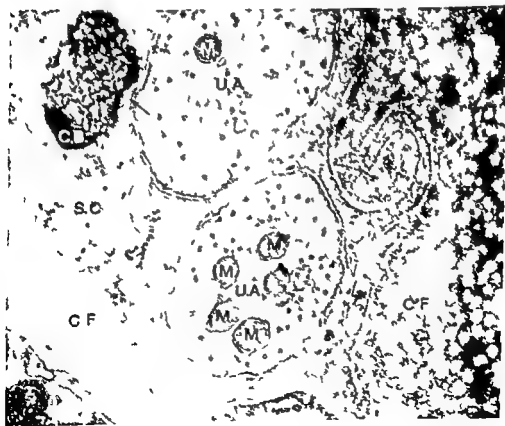


Fig. 8

Enclosed in the cytoplasm of a Schwann cell belonging to an unmyelinated fiber there is a curvilinear body (x41 000). CB = curvilinear body, CF = collagen fiber, M = mitochondria, UA = unmyelinated axon, N = nucleus of a Schwann cell.

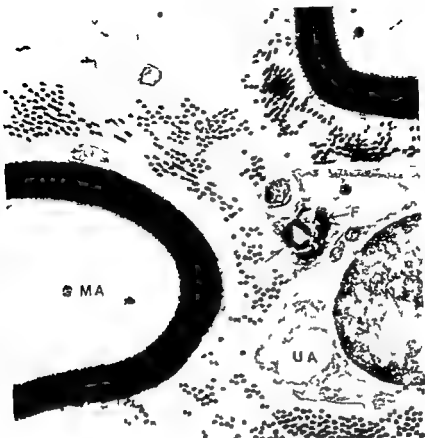


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Fig 5

Fingerprint body ($\times 130\,000$) shows a typical lamellar pattern Abbreviation see Fig 3

Discussion

The lipid pigment which Borst (1922) called lipofuscin had already been demonstrated in 1842 by Hannover in the nervous system Stabel showed its autofluorescent properties in 1911 Lillie et al (1941) and Levine (1968) proposed the name ceroid because of analogy with the lipopigment seen in liver cells after a deficient diet had resulted in liver cirrhosis

In 1969 Zeman et al proposed the use of the term neuronal ceroid lipofuscinosis to which is mentioned above some cases of the late infantile juvenile and adult AFI must be related He separated this group for the following reasons they all showed an accumulation of ceroid lipofuscin material an accumulation of a specific lipid could not be shown a serious neuron loss occurred

as a result of an undefined cellular process and a lysosomal enzyme defect could not be shown. The chemical composition of the mentioned autofluorescent pigment remains unknown. Zeman et al (1970) suggested that a disturbance in the peroxidation mechanism of poly unsaturated fatty acids must be sought as the basis of this disease. The reactive site thus liberated was suggested to react with biochemically active molecules (among others phospholipids, cerebrosides) and thus be responsible for the formation of ceroid lipofuscin and neuron loss. Ultrastructural investigation of these cells has shown that these pigment granules show a characteristic structure which possesses according to Elfenbein (1969) and Gonatas (1969) a certain specificity with regard to the subtypes of Batten's disease. Thus the mentioned investigators thought that curvilinear bodies occur more often in the late infantile form and fingerprint bodies more often in the juvenile form.

Based on these findings as well as on the clinical symptoms we can assign our first patient to the late infantile AFI and the second patient to the juvenile AFI. The question remains though whether the characteristic ultrastructural findings are specific to these subtypes of Batten's disease.

The electron microscopic investigation of the sural nerve in this disease in which Carpenter (1972) for the first time described the above mentioned pigments appears to involve a relatively harmless operation to obtain the necessary material in contrast to brain biopsy, appendectomy and rectum biopsy and appears to be an important addition to the early diagnosis of Batten's disease because as is the case with our second patient the visual disturbances based on fundus abnormalities are the most predominant.

Moreover such an investigation may enable us to place a positive meaning on the more or less characteristic fundus abnormalities which have been described in the literature in the course of the years in other words certain fundus abnormalities may fit a certain morphological abnormality in the neurons and vice versa.

The question remains why we at present prefer a sural nerve biopsy to the more simple skin biopsy or the lymphocyte examination.

When the question is specifically whether we are dealing with a ceroid lipofuscinosis or not a skin biopsy or a lymphocyte examination can be used. If this is not the case and there is an ill understood disorder of the nervous system the sural nerve biopsy is preferable because a wider field of diseases can be covered (among others metachromatic leukodystrophy, globoid cell leukodystrophy, Caucher's disease, disease of Niemann-Pick, Seitelberger's disease, the Chediak-Higashi syndrome). In other cases when storage material is absent changes observed in neuropathies can provide the right diagnosis.

We suppose that an interdisciplinary approach to the above mentioned

fundus abnormalities will provide a positive advantage in allowing a better understanding of these abnormalities

A systematic division and description of the fundus abnormalities only without a thorough general internal neurological biochemical and if necessary supplementary (ultra) microscopic investigation will not provide a real advantage in the penetration of the abnormalities since these must be seen as a component of a complex disease with a (sometimes isolated) ocular manifestation

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a theoretical and from a practical aspect Demonstration of trigeminal nerve hypaesthesia is employed as an aid in neuro ophthalmologic diagnostics Hypaesthesia is present in about 50 per cent of contact lens wearers (Edmund 196) This hypaesthesia plays a role in the adaptation and probably also as regards complications In corneal transplantation re innervation is a favourable diagnostic sign Recurrent dendritic keratitis is associated with increasing hypaesthesia (Horn 1970) Hypaesthesia is present in cases of zoster and in tractable glaucoma and after operation for retinal detachment

Sensitivity declines with increasing age (Boberg Ans 1952 1955 Forsius 1956) and at low external temperatures (Kolstad 1970)

The sensitivity is the highest in the corneal centre and decreases towards the periphery The vertical meridian is less sensitive than the horizontal

The *corneal nerves* branch off from the ciliary nerve They pass from the suprachoroidal space into the sclera just behind the limbus The great majority of the nerve branches pass radially from the sclera into the cornea while only few come from the subconjunctival region

The *conjunctival nerves* likewise belong to the trigeminal nerve group The nerves leading to the ciliary part of the bulbar conjunctiva come from the ciliary nerve while those to the tarsal conjunctiva and the lid margin are derived from the frontal nasociliary lacrimal and infra orbital nerves

These nerves constitute a plexus in front of the tarsus from which the lid margin is richly supplied with nerves particularly so the mouths of the meibomian glands and the cilia Fewer branches pass to the conjunctiva The nerves end in fine branches in relation to epithelial cells and vessels or they form Krause's end bulbs i.e. sense organ like formations whose function has not yet been clarified

Method

Cheet & Bennet's instrument is used for measuring first the sensitivity of the cornea and thereafter that of the conjunctiva

The patient sits in front of the seated observer Light is thrown on the eye from an adjustable lamp the rays of which can always be adjusted so as to throw optimum light on the different regions to be studied

The observer must use a frontal magnifying glass (myopes the unaided eye)

The patient is requested to fix a point behind and above the observer Then Cheet & Bennet's esthesiometer is approached at a slow rate The nylon thread is of a minimum length (10 mm) The thread kept at right angles to the cornea

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CONJUNCTIVAL SENSITIVITY IN NORMAL EYES

BY

M S NORN

Conjunctival sensitivity has been studied using Cochet & Bonnet's esthesiometer on a series of 102 normal eyes. Measurements were performed on 18 areas of each eye.

The cornea was found to be the most sensitive, after which followed the lid margin. The caruncle was less sensitive and the conjunctiva the least so. The mean values found in the stated four regions were 12 mg, 53-54 mg, 63 mg and 83-96 mg per 0.0113 mm² respectively.

No local differences were noticed within the conjunctiva nor within the lid margin.

Sensitivity declines appreciably with increasing age.

The importance of considering the sensitive lid margin when fitting contact lenses is emphasized.

Key words: conjunctiva - cornea - sensitivity - normal material - contact lenses

Very few investigations of conjunctival sensitivity are available.

Corneal sensitivity on the other hand has been carefully studied by Boberg Ans in his thesis of 1955 and by Cochet & Bonnet in 1961 among others.

Boberg Ans constructed an esthesiometer with a nylon thread of variable length. The same principle is employed in the commercially obtainable Cochet-Bonnet's instrument (from Luneau & Coffignon, Paris). I have found no difference between the two instruments with regard to their use in practice.

As is well known, a study of the corneal sensitivity is of interest both from

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Table I
Adjustment tests on scales of Cochet & Bonnet's esthesiometer

Nylon thread length mm	Mg pressure read in Table	Mg pressure measured on scales
60	11	10-12
55	12	12-14
50	15	15-17
45	16	19-20
40	21	20-22
35	27	29-34
30	36	36-39
25	52	48-52
20	75	60-80

To adjust the esthesiometer used I have pressed its nylon thread against the scale pan of sensitive dispensing scales in the same manner as the thread is pressed against the cornea with a resulting just visible curving at right angles to the surface. The esthesiometer is held in the hand, not fixed.

The pointer of the scales oscillates considerably because it is impossible to keep the esthesiometer quite steady in the hand.

The result of the control testing leaves no suspicion of instrumental error (Table I).

Material

The material investigated comprised 107 normal eyes from 63 subjects. The patients had been referred from other units to the Out Patient Eye Clinic for routine ophthalmoscopy and other examinations. None of the patients suffered from ophthalmic or neurologic diseases.

The age incidence is shown in Table III.

Result

The results of the investigations are illustrated in Fig. 1.

The sensitivity is indicated by the amount of pressure necessary before the patient recognizes the touch. In the diagram are stated pressures in milligrams.

is passed towards the corneal centre and pressed slowly against this point with just enough force that the thread becomes just visibly curved. At this stage the thread must be at exactly right angles to the cornea. According to the directions the curving should make the thread less than 5 per cent shorter or give a less than 4 per cent deviation from a straight line.

If the touch is not perceived by the patient, the test is repeated with a 5 mm shorter nylon thread and so on with shorter and shorter threads until the patient feels the touch (minimum perceptible). The length of this last nylon thread is read.

In case of doubt the test is repeated and the patient should state when he feels the touch. Blinking is not recorded as it often occurs before the patient feels anything (and is therefore unreliable).

The examination must proceed at a slow rate to avoid summation.

After the corneal centre has been tested the patient is to look down. The esthesiometer with maximum thread length is now passed slowly towards the middle of the upper lid margin behind the cilia but in front of the conjunctiva. The thread is pressed perpendicularly against the middle of the margin until it is just visibly curved while the lid is slightly everted with a finger. If nothing is felt the test is repeated with decreasing thread lengths until the patient notices the touch.

The test is repeated medially and laterally on the same lid margin and there after performed at not fewer than three sites superiorly on the bulbar conjunctiva (see Fig. 1).

The patient is now requested to look upwards and the sensitivity is tested on not fewer than three areas of the bulbar conjunctiva below the cornea on three areas of the tarsal conjunctiva and three of the lower lid margin.

The middle of the caruncle is tested for sensitivity with the eye abducted and the lid margin at the site of the outer canthus with the eye adducted.

With their eyes turned in the stated directions the patients cannot see nor consequently be disturbed by the esthesiometer.

Not fewer than 18 localities are tested in each eye.

A different order of testings has been employed in some cases without this having altered the result.

Repeated tests rarely give results differing more than 5 mm from the original value measured at the same site.

In cases of local differences I have aimed at finding the line between areas with different sensitivities.

The result for the individual patient is entered in a diagram where the length of the esthesiometer thread at each site is converted into milligrams per cross section of the nylon thread read from a table.

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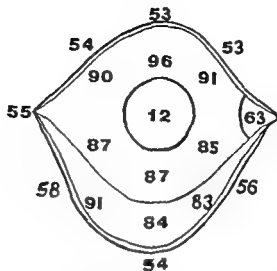


Fig 1

Sensitivity of different areas of conjunctiva and lid margin. Mean values for 10³ normal eyes. The figures indicate the sensitivity in the region concerned expressed in mg/0.0113 mm nylon thread (Cochet & Bonnet's esthesiometer).

corresponding to the nylon thread used which has a diameter of 0.12 mm (area 0.0113 mm²).

The diagram shows the sensitivity to be highest centrally on the cornea and very much lower on the conjunctiva. On the corneal centre the touch is recognizable at a pressure of no more than an average of 12 mg. On the bulbar or tarsal conjunctiva on the other hand pressures ranging between 80 and nearly 100 mg are required before the touch is felt.

The lid margin holds a position intermediate between the cornea and the conjunctiva, its sensitivity being significantly above that of the conjunctiva but significantly below that of the cornea.

The caruncle is more sensitive than the remaining conjunctiva.

The sensitivity seems to be uniform within the entire conjunctival region with the exception of the caruncle.

The upper and lower lid margins are equally sensitive.

In other words no differences have been demonstrated between superior and inferior regions for instance nor between medial and lateral halves.

Standard errors of the mean and measured sensitivities have been set out in Table II given partly in milligrams at the nylon thread thickness employed and partly in grams per square millimetre.

The sensitivities of conjunctiva and lid margin display age determined

Conjunctival Sensitivity in Normal Eyes

Table II

Sensitivities of corneal centre middle of lid margin and middle of conjunctiva (in mg) using nylon thread 0.19 mm in diameter. Corresponding standard error of mean. Last column sensitivity converted into grams per square millimetre.

	Sensitivity mg/0.0115 mm	SEM	Sensitivity g/mm
Cornea	10	0.5	1.06
Upper lid margin	53	3	4.60
Lower lid margin	54	4	4.18
Sup. bulbar conjunct	96	5	8.48
Inf. bulbar conjunct	87	5	7.70
Inf. tarsal conjunct	84	4	7.43

variations similarly as the cornea i.e. the sensitivity declines with increasing age (as shown in Table III and Fig. 2).

In Fig. 2 the upper curve represents the mean sensitivity for nine conjunctival areas in the age group concerned, the middle curve the mean for seven localities of the lid margin and the lower curve the mean of corneal centre measurements on 102 eyes.

Sensitivity measurement on the superior tarsal conjunctiva is unreliable because the everted position of the upper lid makes the patient uncomfortable. Measurement in eight cases gave results suggesting that this area was slightly more sensitive than the remaining conjunctiva.

Table III

Sensitivities of conjunctiva lid margin and cornea dependence on age
10 normal eyes

	≤ 49	40	50	60	≥ 70
Cornea	11	11	1	14	1
Lid margin (areas)	33	40	30	4	69
Cornea	4	56	11	85	6
Conjunctiva (3 areas)	13	8	50	113	90
Conjunctiva lid margin	53	6	69	9	84
Number of patients	5	15	19	11	15

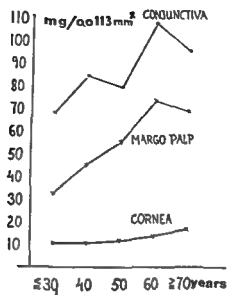


Fig 2

Age dependence of conjunctival sensitivity. The upper curve shows the mean for nine conjunctival areas, the middle curve the mean for seven lid margin localities and the lower curve the sensitivity of the corneal centre (cf Fig 1 concerning the areas). Abscissa: normal subjects' ages (102 eyes). Ordinate: sensitivity in mg/0.0113 mm² nylon thread Cochet & Bonnet's sensibilometer.

The sensitivity of the palpebral skin was generally intermediate between that of the lid margin and that of the conjunctiva (eight cases).

A nerve loop displayed high sensitivity (corresponding to that of the cornea). This raised sensitivity was localized within a small area only of the bulbar conjunctiva, namely the small dark emissary canal of the sclera.

Discussion

The present study of 102 normal eyes showed sensitivity values for the bulbar conjunctiva ranging from 80 to 100 mg.

Boberg & Ans by measuring superiorly, medially and laterally on the bulbar conjunctiva arrived at values ranging from 72 to 200 mg. The values are not directly comparable, however. Boberg & Ans used a nylon thread 0.11 mm in diameter in the esthesiometer constructed by him (0.12 mm in our instrument).

Dixon measured the sensitivities centrally on the cornea at a point centrally on the superior tarsal conjunctiva and at a point on the conjunctiva close to

the upper lid margin of 774 patients prior to contact lens fitting. He found values of 1.0, 50.0 and 130 mg respectively.

The relative sensitivity values for cornea, conjunctiva and lid margin show the same tendency as in the present series, but the absolute values do not agree (different procedures²).

Lowther et al. used a modified Bonnet & Cochet's sensibilometer with manipulator and the extreme 3 mm of the nylon thread bent 70°.

Four persons aged 19–21 years were tested prior to contact lens fitting. The lid margin sensitivity (that of the lower lid measured between mouths of meibomian glands and conjunctiva) was often found to be equal to that of the cornea, i.e. above the maximum perceptibility limit of the instrument.

The above mentioned investigations both gave the result that the sensitivity of the lid margin decreases during wearing of contact lenses. It is pointed out that the lid margin sensitivity plays an important role in the fitting of contact lenses. Particular attention should be given to the relation between contact lens edge and lid margin.

In none of the patients of the present investigation was the lid margin sensitivity as high as that of the corneal centre, but it was higher than that of the conjunctiva. It therefore seems reasonable to stress the importance of considering not only the cornea, but also the lid margin when fitting contact lenses.

Disproportion between the sensitive lid margin and the contact lens will cause difficulties. The patient will compensate for the inconvenience by blinking at longer intervals and less efficiently (non blinkers). This will result in a less adequate renewal of tear fluid under the contact lens with a consequent tendency towards depression of the corneal metabolism – in other words a tendency towards corneal oedema.

The relatively high sensitivity of the caruncle may merit consideration in the fitting of haptic lenses.

Forsius (1955) has shown that corneal sensitivity is reduced in the presence of arcus senilis, also when this is present in fairly young individuals.

The observed markedly declining sensitivity of conjunctiva and lid margin with increasing age shows that other factors likewise play an important role in the age determined sensitivity reduction.

The few available investigations into conjunctival sensitivity are difficult to compare owing to the use of different instruments and different units of measurement (millimetres nylon thread, milligrams per thread area of different diameters or grams per square millimetre).

The commercially obtainable Cochet & Bonnet's esthesiometer with a thread diameter of 0.12 mm was used in the present study. The results were converted into mg/0.0113 mm and g/mm² (Table II).

The material under review may therefore be employed as a normal material. Allowance must be made however for the patient's age. This is done by comparing the measured value with Fig. 2 or Table III.

Investigations into conjunctival sensitivity under pathological conditions will be published in a future paper.

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OCCURRENCE OF MENTAL RETARDATION IN PATIENTS WITH RETINOBLASTOMA

BY

AHTI TARKKANEN

In a series of 10³ consecutive patients with retinoblastoma five were mentally retarded. These were classified as showing debility in two cases and idiocy/imbecility and unclassified mental retardation in one case each. Three of the five patients had bilateral retinoblastoma and two had a positive family history for retinoblastoma. One of the patients had a congenital heart defect and another had a deformed skull. As occasionally retinoblastoma and a deletion of the long arm of a D chromosome are seen in combination with mental retardation the present findings support the opinion that the association of retinoblastoma and mental retardation may represent a variant of the D deletion syndrome. Retinoblastoma patients deserve a complete physical and mental evaluation and the ones exhibiting disorders merit cytogenetic studies.

Key words: retinoblastoma - idiocy - imbecility - debility - mental retardation

The general physical findings of patients with retinoblastoma are usually reported as normal. In 1931 however Falls & Neel called attention to the association of mental defects and retinoblastoma. They found mental defects in five out of 73 retinoblastoma patients. No other significant association of retinoblastoma with ocular physical or mental characteristics was noted. Taklikos (1964) observed a 3 per cent incidence of mental defects in retinoblastoma patients compared to the 0.3 per cent found among children of the same age in Great Britain. In addition single cases have been reported by

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BY

AHTI TARKKANEN

In a series of 107 consecutive patients with retinoblastoma five were mentally retarded. These were classified as showing debility in two cases and idiocy/imbecility and unclassified mental retardation in one case each. Three of the five patients had bilateral retinoblastoma and two had a positive family history for retinoblastoma. One of the patients had a congenital heart defect and another had a deformed skull. As occasionally retinoblastoma and a deletion of the long arm of a D chromosome are seen in combination with mental retardation, the present findings support the opinion that the association of retinoblastoma and mental retardation may represent a variant of the D deletion syndrome. Retinoblastoma patients deserve a complete physical and mental evaluation and the ones exhibiting disorders merit cytogenetic studies.

Key words: retinoblastoma idiocy - imbecility - debility - mental retardation

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Herm & Heath (1956) and by Jensen (1965) The significance of this association became apparent after partial deletion of the long arm of the D chromosome had been described in children with retinoblastoma (Allerdice et al 1969 Taylor 1970 Thompson & Lyons 1965 Wilson et al 1969) In two children slow development was the principal abnormality and in this way the syndrome of retinoblastoma and mental retardation may represent a variant of the D deletion syndrome (Jensen & Miller 1971) In addition to mental defects, pathological manifestations of the central nervous system also have been described in retinoblastoma patients Taktikos (1964) reported three patients in whom retinoblastoma was associated with mental defects and congenital hydrocephalus The case of Thompson & Lyons (1965) had unilateral retinoblastoma with microcephalus

The purpose of this communication is to report further cases of retinoblastoma associated with mental defects

Clinical Observations

Diagnostic criteria The diagnosis of retinoblastoma was confirmed by histopathological examination in every case The specimens primarily studied elsewhere were reviewed by the author The diagnoses of mental defects were made by the pediatricians Routine assessment of the mental status of the patients was not conducted and therefore only the very obvious cases were diagnosed It is possible that minor mental defects escaped the survey because of the difficulty of evaluating mental status at the usual retinoblastoma age

Mental defects During the period of observation 102 new cases of retinoblastoma were diagnosed in Finland Of them five were classified as mentally retarded Clinical data of these patients have been presented in Table I The sex and age distribution of the patients did not differ from the normal for patients with retinoblastoma The occurrence of bilateral retinoblastoma in three of the five cases is noteworthy as is case 2 a debile who had bilateral retinoblastoma with positive family history The mental defects were debility in two cases and idiocy imbecility and unclassified mental retardation in one case each Other pathological findings were one congenital heart defect and one deformed skull

The mental status of the patients may have contributed to the delayed evaluation of the ocular condition Cases 1 and 5 had had ocular symptoms since birth but were first brought to an ophthalmologist at the ages of 3¹/₂ and 4 years respectively Similarly three of the five patients died of metastases within short periods after the treatment was started

Telle I
Data of five mentally retarded patients with retinoblastoma in a series of 102 retinoblastoma patients

No	Sex	Age at onset of treatment	Family history of retino blastoma	Eye involved	Treatment	Cour #	Mental defect	Other pathology
1	F	3 1/2	Yes	OD	Enucleation OD Radiation OD	Died of metastases at the age of 4 years	Debility	
2	M	2 1/2	Yes	OU	Enucleation OD Radiation OS	Died of metastases at the age of 4 years	Debility	
3	M	1/2	No	OU	Enucleation OS Radiation OD	Alive at the age of 4 1/2 years without recurrences	Idiocy	Deformation of the skull
4	F	1	No	OU	Enucleation OD Radiation OS	Died of metastases at the age of 2 1/2 years	Imbecility	Congenital heart defect
5	F	3	No	OS	Enucleation OS	Alive at the age of 10 years without recurrences	Unclassified mental retardation	

Herm & Heath (1956) and by Jensen (1965) The significance of this association became apparent after partial deletion of the long arm of the D chromosome had been described in children with retinoblastoma (Allerdice et al 1969 Taylor 1970 Thompson & Lyons 1965 Wilson et al 1969) In two children slow development was the principal abnormality and in this way the syndrome of retinoblastoma and mental retardation may represent a variant of the D deletion syndrome (Jensen & Miller 1971) In addition to mental defects pathological manifestations of the central nervous system also have been described in retinoblastoma patients Traktikos (1964) reported three patients in whom retinoblastoma was associated with mental defects and congenital hydrocephalus The case of Thompson & Lyons (1965) had unilateral retinoblastoma with microcephalus

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Table I
Data of 50 mentally retarded patients with retinoblastoma in a series of 10 retinoblastoma patients

No	Sex	Age at onset of treatment	Family history of retino blastoma	Eye involved	Treatment	Curr #	Mental defect	Other pathology
1	F	3 1/2	Yes	OD	Enucleation OD Radiation OD	Died of metastases at the age of 4 years	Debility	
2	M	2 1/2	Yes	OU	Enucleation OD Radiation OS	Died of metastases at the age of 4 years	Debility	
3	M	1 1/2	No	OU	Enucleation OS Radiation OD	Alive at the age of 4 1/2 years without recurrences	Idiocy	Deformation of the skull
4	F	1	No	OU	Enucleation OD Radiation OS	Died of metastases at the age of 2 1/2 years	Imbecility	Congenital heart defect
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Discussion

Bilateral involvement is found in about 30% of retinoblastoma cases and is probably always caused by an autosomal dominant gene while unilateral retinoblastoma is not usually inherited. In this respect it has to be noted that three of five cases of the present series had bilateral involvement and one of them had a family history of retinoblastoma. In the series of Taktikos (1964) eight of the nine cases had bilateral involvement. Similarly, the mentally retarded cases of Herm & Heath (1956) as well as of Jensen (1965) had bilateral retinoblastoma. In spite of the absence of family history for retinoblastoma, the frequent bilateral involvement would favor the genetic background of the association between retinoblastoma and mental retardation.

In a case reported by Orye et al (1971) the patient with bilateral retinoblastoma and a deletion of the long arm of a D chromosome had bilateral clinodactyly and cleft uvula but no mental retardation. However, in the wide array of malformations reported in D deletion syndrome, mental retardation frequently has been found (Jensen & Miller 1971) and there have been two cases of D deletion syndrome with retinoblastoma and mental retardation (François et al 1972). Hence, mental retardation with retinoblastoma may represent a variant of this chromosomal disorder (Miller & Jensen 1971). It would seem that every patient with retinoblastoma deserves a comprehensive physical and mental evaluation, and the ones exhibiting disorders merit cytogenetic studies.

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$$m = \frac{\pi d}{2\lambda} \sin v \quad (1)$$

$$I = \left[\frac{\pi d}{4} - \frac{J_1(2m)}{m} \right] \quad (2)$$

Here I is the intensity of light in a point of the diffraction pattern v is the angular distance from the centre of the pattern to this point d is the diameter of the circular aperture and λ is the wave length of the light

$J_1(2m)$ is Bessel's function of order unity m is an intermediate variable defined by eq (1)

The infinite series $\frac{J_1(2m)}{m}$ is convergent for all values of m and passes al

ternately through positive and negative values as m increases from zero The intensity consequently presents maximum and zero values The detailed calculation of the diffraction pattern presents no difficulties as the values of Bessel's functions are available in tables Lommel (1886) has published tables

where the values of $\frac{J_1(2m)}{m}$ and $\left[\frac{J_1(2m)}{m} \right]^2$ are given to six decimal places

The bright rings are very faint the first and brightest has a maximum intensity of 1.75% of that of the central spot and it seems that the rings can be disregarded in a discussion of the resolving power The angular radius of the central bright spot and that of the first dark ring is given by the equation

$$\sin v = 1.22 \frac{\lambda}{d} \quad (3)$$

When two very close point sources of light are viewed their diffraction patterns will overlap and they cannot be distinguished as distinct sources if the overlapping of the central spots exceeds a certain limit The two patterns are said to be resolved when the central maximum of one falls on the first dark ring of the other The angular distance between the sources is then given by eq (3)

This is Rayleigh's criterion and a useful standard method for studying the resolving power of many optical instruments

Rayleigh's criterion can be applied to the human eye It is exactly applicable only to optical systems where the stop is in front of or coincides with the first refracting surface In the human eye we can get an approximate value by sub

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DIFFRACTION AND VISUAL RESOLUTION I The Resolution of Two Point Sources of Light

BY

ULF HALLDÉN

Diffraction is generally regarded as the limiting factor of visual resolution at least when the diameter of the pupil is less than 2.5 mm. This does not agree well with the clinical experience that it is not unusual for patients treated with miotics who have a pupil diameter of less than 1 mm to have normal visual acuity. A quantitative discussion of the diffraction pattern of a circular aperture and of the Stiles Crawford effect gives no adequate explanation of this discrepancy.

Key words: diffraction pattern of a circular aperture - Rayleigh's criterion - Stiles Crawford effect - Young's theory of diffraction

When a point source of light such as a distant star is viewed through a telescope the light wave falling upon the objective is limited by a circular aperture. If this aperture is small instead of having a point image of the source as geometrical optics would lead us to expect there is a diffraction pattern which consists of a bright central spot surrounded by a series of alternately bright and dark rings. This diffraction pattern is important as it can be applied to the resolving power of many optical instruments including the human eye.

The calculation of the pattern is unfortunately a problem of considerable difficulty since it requires a double integration over the surface of the aperture. The problem was first solved by Airy (1834). The result can be presented as two equations

$$m = \frac{\tau d}{2\lambda} \sin v \quad (1)$$

$$I = \left[\frac{\tau d}{4\lambda} \frac{J_1(2m)}{m} \right]^2 \quad (2)$$

Here I is the intensity of light in a point of the diffraction pattern v is the angular distance from the centre of the pattern to this point d is the diameter of the circular aperture and λ is the wave length of the light

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Rayleigh's criterion can be applied to the human eye It is exactly applicable only to optical systems where the stop is in front of or coincides with the first refracting surface In the human eye we can get an approximate value by sub

stituting in the formula the diameter of the entrance pupil. The angle α is so small that it is sufficiently accurate to substitute the angle itself in place of its sine. If the angle α expressed in minutes it becomes identical at the limit of resolution with the minimum separable, which is the reciprocal of the visual acuity (V). If for the wave length we choose that of sodium light 589 nm eq. 3 gives

$$V = 0.404 d \quad (4)$$

This result means that visual acuity is limited by diffraction with ordinary pupil diameters. If the diameter of the pupil is 2.5 mm V cannot exceed 1.0 and a pupil diameter of 1.0 mm will give a maximum value of V of 0.4. This is the generally accepted conclusion given in the standard textbooks (eg Helmholtz 1962 I pp 196-197 440-442 Ogle 1968 p 193 Stenström 1964 p 11) but it does not agree with practical experience. Among patients treated with miotics who have a pupil diameter of less than 1.0 mm it is not unusual to find a visual acuity of 1.0. The purpose of the present paper is to discuss this discrepancy.

The Rayleigh Criterion

The Rayleigh criterion is a conventional measure designed and used more for comparing the resolving powers of optical instruments than to find an absolute

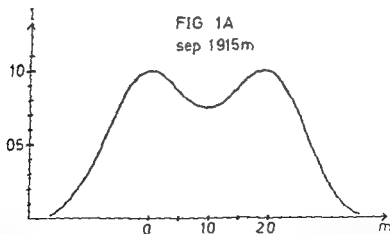


Fig 1A-E

Summation curves for different separations 1A the Rayleigh criterion. When two diffraction patterns overlap the intensity of light in each point is equal to the sum of the intensity in that point of each of the patterns. Abscissae in m units defined by eq. (2). Ordinates relative intensities of light.

limit It might be possible that the criterion is generous and that the absolute limit of resolution is less than the Rayleigh criterion

When two diffraction patterns overlap the intensity of light in each point is equal to the sum of the intensities in that point of each of the patterns Such a summation for the Rayleigh criterion is shown in Fig 1A There are two maxima and between them a minimum The intensity at the maxima is 1 000 and at the minimum 0 736 This difference in intensity is very easily observable The angular distance between the maxima is equal to that between the centres of the patterns

FIG 1B

sep 18m

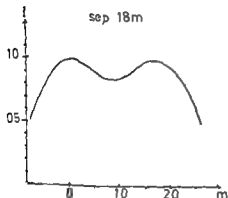


FIG 1C

sep 17m

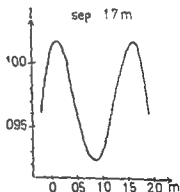


FIG 1D

sep 16m

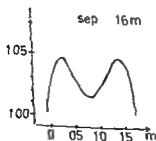
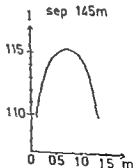


FIG 1E

sep 14.5m



If the separation is reduced the intensity at the minimum will increase more than that at the maxima. At the same time the angular distance between the maxima will be progressively less than that between the centres of the patterns. Finally the minimum disappears completely. To demonstrate this a number of curves of summation have been calculated and some of them have been reproduced (Fig. 1B-E). The calculation of the curves is not difficult and if the tables of Lommel (1886) are used it is not even very laborious.

The separations have been measured in units of m which is advantageous as the validity of the curves is not influenced by the wave length of the light or by the diameter of the stop. If the wave length and the diameter are known m can be transformed to minutes of angle using the equation

$$v = 2190 m \frac{\lambda}{d} \quad (5)$$

The ordinates of the curves have been drawn to different scales to visualise the minima. The result is summarized in Table I.

The density of foveal cones and the sensitivity of the cones for differences of luminous intensity is such that it is very probable that the limit of resolution is better than that given by Rayleigh's criterion but it is difficult to arrive at an exact figure. It is easier to find a value below which no resolution is possible. If the m value of the distance between the centres of diffraction patterns is 1.45 or less there will be no minimum and consequently no resolution. If this figure is put into eq. (4) the following inequality is found

$$V < 0.53 d \quad (6)$$

Table I

Distance in m units between centres of diffraction patterns	Distance in m units between maxima	Difference in intensity $\frac{I_{\max} - I_{\min}}{I_{\max}}$
1.915 (Rayleigh crit.)	1.915	0.764
1.8	1.7	0.168
1.7	1.5	0.093
1.6	1.2	0.031
1.55	0.85	0.010
1.50	0.4	0.0004
1.45	no minimum	

This does not differ much from eq (4) and gives no sufficient explanation of the discrepancy discussed

THE IMPORTANCE OF THE STILES-CRAWFORD EFFECT

The retinal cones are directionally sensitive (Stiles & Crawford 1933) Light rays entering the pupil centrally and reaching the cones along their axes produce a greater visual stimulation than light entering the periphery of the pupil and falling obliquely on the cones. The quantitative aspect of this has been investigated and Stiles & Crawford have represented the results in an empirical formula

$$\lg H = -ar \quad (7)$$

where a is a constant r is the distance in mm between two points in the pupil one the point which the light must pass to have maximum directional efficiency the other the point where the relative directional efficiency is H

This directional sensitivity will reduce the effect of diffraction and improve the resolving power of the eye (Bárány 1946). We will now try to find a quantitative measure of this improvement

Equations (1) and (2) give the intensity of light in every point of the pattern of diffraction but they give no information on the direction of light. This is a consequence of the fact that the equations were found by integrations over the surface of the aperture

There is another way of treating diffraction which might give a possibility of finding a diffraction pattern corrected for the direction of light. This starts from Young's theory of diffraction that the diffraction patterns are due to interference between the direct beam and a wave from the edges of the stop (Rubinowicz 1957 Ditchburn 1963 pp 162 and 171 Rubinowicz 1966). The first termed the direct incident wave defined in the sense of geometrical optics is described by the wave function of undisturbed propagation of light. The second wave termed the diffracted wave is represented by a wave diverging from the illuminated edge of the stop. The diffracted wave at the boundary of the shadow suffers a sudden change of phase of magnitude π . The amplitudes of the diffracted wave on either side of the boundary of the shadow are equal to half the amplitude of the incident wave.

This is Young's diffraction theory and is fully equivalent with that of Fresnel but the latter has the advantage that it is precisely formulated by Kirchhoff's surface integral over the diffracting aperture. The amplitudes and phases of the two waves of Young's theory are known and it is possible to formulate the wave functions and to calculate diffraction patterns. For the

If the separation is reduced, the intensity at the minimum will increase more than that at the maxima. At the same time the angular distance between the maxima will be progressively less than that between the centres of the patterns. Finally, the minimum disappears completely. To demonstrate this a number of curves of summation have been calculated and some of them have been reproduced (Fig. 1B-E). The calculation of the curves is not difficult and if the tables of Lommel (1886) are used it is not even very laborious.

The separations have been measured in units of m which is advantageous as the validity of the curves is not influenced by the wave length of the light or by the diameter of the stop. If the wave-length and the diameter are known m can be transformed to minutes of angle using the equation

$$v = 2190 m \frac{\lambda}{d} \quad (5)$$

The ordinates of the curves have been drawn to different scales to visualise the minimum. The result is summarized in Table I.

The density of foveal cones and the sensitivity of the cones for differences of luminous intensity is such that it is very probable that the limit of resolution is better than that given by Rayleigh's criterion but it is difficult to arrive at an exact figure. It is easier to find a value below which no resolution is possible. If the m value of the distance between the centres of diffraction patterns is 1.45 or less there will be no minimum and consequently no resolution. If this figure is put into eq. (4) the following inequality is found

$$V < 0.53 d \quad (6)$$

Table I

Distance in m units between centres of diffraction patterns	Distance in m units between maxima	Difference in intensity $\frac{I_{\max} - I_{\min}}{I_{\max}}$
1.915 (Rayleigh crit.)	1.915	0.264
1.8	1.7	0.168
1.7	1.5	0.093
1.6	1.2	0.031
1.55	0.95	0.010
1.50	0.4	0.0004
1.45	no minimum	

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special case of Fraunhofer diffraction the functions can be found in Rubinstein (1966) p 215 eq (10.7) p 219 eq (10.18)

The retinal cones are less sensitive to the diffracted wave which diverges from the edge of the pupil and falls obliquely on the cones than to the direct incident wave which passes the pupil and reaches the cones more or less along their axes. It is possible to calculate a factor of correction which measures this directional sensitivity. This factor of correction is found from eq (1) by dividing the relative directional efficiency of the diffracted wave with that of the direct incident wave. The value of r for the diffracted wave in eq (1) is equal to the radius of the pupil = $d/2$. The r value of the direct incident wave is not equal to zero as this wave passes through all parts of the pupil. The median r value is given by the radius of a circle with half the surface of that of the pupil = $d/2\sqrt{2}$. The correction factor for the intensities (k) is consequently given by the expression

$$\lg k = -a \left(\frac{d}{2} \right)^2 + a \left(\frac{d}{2\sqrt{2}} \right)^2$$

or simplified

$$\lg k = -\frac{1}{8} a d^2 \quad (8)$$

As the numerical value of the constant a is about 0.05 for a wave length of 0.00059 mm it is now possible to find approximate numerical values of k for different values of d (Table II)

Diffraction is important as the limiting factor of visual resolution when the diameter of the pupil is small. In such a case the value of k does not differ much from unity. It is evident that the improvement of visual resolution caused by the Stiles Crawford effect is very slight.

Table II

d mm	k
1.0	0.986
1.5	0.963
2.0	0.944
2.5	0.914
3.0	0.878
4.0	0.794

This report deals with a case of angle closure glaucoma in which frequent prodromal attacks were released by Yoga exercises. Darkroom test was negative but substantial rises in intraocular pressure invariably followed the prone position test (Hyams et al 1968 Kalthoff 1971 Harris et al 1972). Hyams et al suggested that lying in a prone position probably increases pupillary block in eyes disposed to angle closure glaucoma by causing the lens to fall onto the iris. The present study has attempted to confirm this suggestion by using ultrasonographic measurements.

Case Report

A 47 year old female attended the Eye Clinic of Kommunehospitalet on July 1971 because of episodes with blurred vision and rainbow halos predominantly in the left eye. The attacks occurred in evenings after Yoga exercises (including shoulder standing position and prone positions see Fig. 1) and recovered spontaneously during the night's sleep. She had never experienced any eye trouble before she started Yoga half a year earlier. We found visual acuity 6/6 for both eyes which were emmetropic, normal visual fields and ophthalmoscopic fundus appearance, clear cornea and lens by slit lamp examination, intraocular tension (Goldmann applanation tonometry) in the area 15-20 mmHg. Anterior chambers seemed flat and chamber angles narrow by gonioscopy. Water drinking test caused a borderline rise (right eye 6 mm, left eye 9 mmHg) in intraocular tension which however showed no increase during darkroom test.

Yoga tests were now performed in the two relevant positions. First

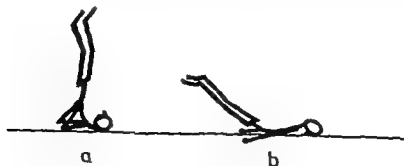


Fig. 1

Some of the Yoga exercises performed by the patient: a) Sarvanghasana
b) Salabhasana (a prone position)

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YOGA-INDUCED ATTACKS OF ACUTE GLAUCOMA

A Case Report

BY

J A FAHMY and H FLEDELIUS

Yoga exercises caused prodromal attacks of acute glaucoma in a previously healthy patient with narrow anterior chamber angles. Attention is drawn to the prone position test which was extremely positive. Ultra sound oculometry confirmed the shallow chamber and thick lens characteristic of primary angle closure glaucoma and supported a gravitational shift of lens position in the prone position.

Key words: Yoga - glaucoma - primary angle closure - prone position test - ultrasonography - oculometry - lens position alteration

Yoga is a religious philosophical discipline the aim of which is complete control of the body rendering the soul free from physical interference.

Since 1960 Yoga has been listed as index word in the Cumulative Index Medicus. The system has been utilized by psychologists and in physiological research into respiratory phenomena and haemodynamics.

As far as we know only one report on accidental injury due to Yoga has been published (Corrigan 1969). It dealt with a fatal case of air embolism in a young girl after breathing exercises performed however in such a manner that the Yoga can hardly be blamed.

This report deals with a case of angle closure glaucoma in which frequent prodromal attacks were released by Yoga exercises. Darkroom test was negative but substantial rises in intraocular pressure invariably followed the prone position test (Hyams et al 1968 Kalthoff 1971 Harris et al 1972). Hyams et al suggested that lying in a prone position probably increases pupillary block in eyes disposed to angle closure glaucoma by causing the lens to fall onto the iris. The present study has attempted to confirm this suggestion by using ultrasonographic measurements.

Case Report

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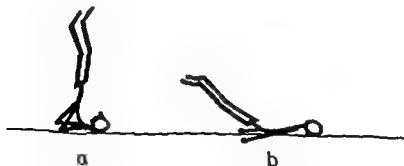


Fig 1

Some of the Yoga exercises performed by the patient. a) Sarvanghasana
b) Salabhasana (a prone position)

shoulder standing for one hour caused no elevation of tonometric readings. A considerable increase however occurred after one hour in a prone position – as suggested by Hyams – on a couch in a well illuminated room. Tonometric readings increased 22 mm for the right eye (20–42 mmHg) and 27 mm for the left eye (18–45 mmHg). One hour after conclusion of the test readings were about 30 mmHg and had not returned to basic levels thirty minutes later. Pilocarpine eyedrops normalized the tension. The patient was held under observation without any treatment.

As time went on attacks also occurred spontaneously. In November a diurnal tension curve showed a substantial rise in the evening (15–48 mmHg). An antiglaucomatous iridectomy was made in the left eye and two months later in the right eye. A new prone position test half a year later was negative.

Ultrasonographic measurement

The time amplitude technique has been reported in detail elsewhere (Fiedelius 1970). The advantage of the employed contact glass is that it – in contrast to other types of liquid filled coupling devices – does not indent the corner of the measured eye. In the usual supine position with topical Novesin anesthesia Methocel in the contact glass and a 10 Mc Ultrasonolux transducer the following results were obtained in two separate days in October 1971 (Table I).

In the prone position however it was not possible to measure in the same way since the Methocel would run out of the contact glass allowing air bubbles to enter and hinder the passage of ultrasound. Thus ideal measurements of the anterior eye segments could not be obtained and compared with the above supine results. We therefore contented ourselves with evaluating only

Table I
Ultrasonographic measurements in supine position (without eye drops except Novesin (I) and in Cyclogyl mydriasis (II))

	Right eye		Left eye	
	I	II	I	II
Depth of anterior chamber (including central corneal thickness) in mm	2.6	2.8	2.8	2.8
Lens thickness (in mm)	4	4	4.1	4.7
Vitreous length (in mm)	16.2	16.1	16.1	16.1
Axial length (in mm)	23.5	23.6	23.6	23.6

vitreous length in the supine and prone positions using a direct method with the transducer coupled to the corneal surface through a drop of Methocel care fully trying not to indent the cornea with the sound probe. Five polaroid photos were taken in each position. They showed that axial vitreous length was about 0.0-0.5 per cent longer in the prone position after one hour than in the initial supine position. This suggested a forward displacement of the lens, the anterior chamber depth was presumed to be reduced correspondingly i.e. by about 0.3-0.4 mm.

Discussion

Lowe stated (1972) that there is a considerable overlap between the oculometric axial parameters of normal eyes and eyes with angle closure glaucoma. Shallow anterior chamber accordingly do not invariably lead to development of the disease. This emphasizes the importance of the trigger mechanism acting in conjunction with the inherent anatomical features. In our case the trigger was Yoga exercise which thereby did not exactly render the soul free from physical interference.

A study by Tarkkanen & Leiskö (1961) demonstrated significant postural variations of the intraocular pressure parallel to alterations in the hydrostatic pressure of the blood column above the eye. This mechanism however does not explain the rise of eye tension following the prone position. Hyams et al (1963) suggested a relative pupillary block caused by a forward movement of the lens against the iris separating a modest rise of tension in normal eyes from a significant rise (at least 8 mmHg) in eyes with angle closure glaucoma. The usefulness of the prone position test in angle closure glaucoma has been further supported by Kalthoff (1971) and recently by Harris & Galin (1972). In addition to the actual rise of tension Kalthoff (1971) also emphasized the time passing until initial tension values returned. According to both criteria the reaction of our patient was extremely positive and the angle closure type of glaucoma was confirmed by the further clinical course.

Ultrasonnd oculometry accordingly showed flat anterior chambers (9.8 mm including corneal thickness) and thick lenses (4.7 mm). Mean values for normal women of equal age are about 3.4-3.5 mm for anterior chamber and 4.1 mm for axial lens thickness (Jansson 1963 among others). Lowe (1972) proposed an upper threshold value of 2.5 mm anterior chamber depth (corneal thickness 0.5 mm not included) which should cover 99.8% of cases of angle closure glaucoma. Our case fits this category after subtraction of corneal central thickness.

The limitations of the commercially available ultrasound equipment (Baum 1967) and the rather primitive technique necessitated in this study must be borne in mind when assessing the position related differences in vitreous length found in our patient. More elaborate equipment is desirable (Coleman et al 1969) when such small shifts in lens position are to be established in individual patients; in addition further difficulties are caused by the prone position. With these problems unsolved we did not extend this ultrasound study to a whole series of patients.

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DAS DOPPELBLITZ ERG BEI DER DIABETISCHEN RETINOPATHIE

VON

H GLIEM D E MÖLLER und G KIETZMANN

Das Doppelblitz ERG von 105 Diabetikern mit einer Retinopathie verschiedenen Stadiums verglichen mit gesunden Probanden bestätigt unsere Erfahrungen mit dem Einzelblitz ERG dass die diabetische Retinopathie die photopische Komponente im ERG schädigt Selbst in fortgeschrittenen Stadien bleibt die skotopische Komponente unbeteiligt Dieses Verhalten ist bereits beim einzelnen Patienten zu beobachten Das Doppelblitz ERG eignet sich zur Frühdiagnostik und Verlaufskontrolle da bereits in Frühstadien der Erkrankung Veränderungen der zweiten photopischen Antwort zu erkennen sind Als mögliche Ursache wird eine Störung im Schaltmechanismus der Ganglienzellschicht angesehen

Key words: electroretinography - double flash - diabetes - retina

In einer früheren Arbeit über die bioelektrische Aktivität der Netzhaut bei der diabetischen Retinopathie (Gliem Möller & Kietzmann 1971) berichteten wir über eine deutliche Minderung der photopischen Aktivität im Gegensatz zur skotopischen Dieses unterschiedliche Verhalten wurde mit fortschreitendem Retinopathiegrad immer deutlicher ebenso wie die Unterdrückung des oszillatorischen Potentials Auf der Suche nach einer klinisch anwendbaren und einfachen elektrophysiologischen Untersuchungsmethode mit der jener Befund für die Beurteilung von Einzelfällen herangezogen werden kann interessierte uns die Doppelblitzmethodik

Entstanden im Rahmen des Forschungsprojektes *Diabetes mellitus*

Eingegangen Oktober 4 1972

The limitations of the commercially available ultrasound equipment (Baum 1967) and the rather primitive technique necessitated in this study must be borne in mind when assessing the position related differences in vitreous length found in our patient. More elaborate equipment is desirable (Coleman et al 1969) when such small shifts in lens position are to be established in individual patients. In addition further difficulties are caused by the prone position. With these problems unsolved we did not extend this ultrasound study to a whole series of patients.

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DAS DOPPELBLITZ ERG BEI DER DIABETISCHEN RETINOPATHIE

VON

H. GLIEM, D. E. MÖLLER und G. KIETZMANN

Das Doppelblitz ERG von 103 Diabetikern mit einer Retinopathie verschiedenen Stadiums verglichen mit gesunden Probanden bestätigt unsere Erfahrungen mit dem Einzelblitz ERG, dass die diabetische Retinopathie die photopische Komponente im ERG schädigt. Selbst in fortgeschrittenen Stadien bleibt die skotopische Komponente unbeteiligt. Dieses Verhalten ist bereits beim einzelnen Patienten zu beobachten. Das Doppelblitz ERG eignet sich zur Frühdiagnostik und Verlaufskontrolle, da bereits in Frühstadien der Erkrankung Veränderungen der zweiten photopischen Antwort zu erkennen sind. Als mögliche Ursache wird eine Störung im Saltmechanismus der Ganglienzellschicht angesehen.

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In einer früheren Arbeit über die bioelektrische Aktivität der Netzhaut bei der diabetischen Retinopathie (Gliem, Möller & Kietzmann 1971) berichteten wir über eine deutliche Minderung der photopischen Aktivität im Gegensatz zur skotopischen. Dieses unterschiedliche Verhalten wurde mit fortschreitendem Retinopathiegrad immer deutlicher, ebenso wie die Unterdrückung des oszillatorischen Potentials. Auf der Suche nach einer klinisch anwendbaren und einfachen elektrophysiologischen Untersuchungsmethode mit der jener Befund für die Beurteilung von Einzelfällen herangezogen werden kann, interessierte uns die Doppelblitzmethodik.

Entstanden im Rahmen des Forschungsprojektes Diabetes mellitus

Eingegangen Oktober 24 1972

Das Doppelblitz Elektretinogramm (DB ERG) der gesunden Netzhaut

Während die erste elektretinographische Antwort (A_1) nach einer Doppelstimulation mit kurzem Intervall unter Dunkeladaptationsbedingungen vorwiegend durch skotopische Eigenschaften charakterisiert ist, weist die zweite eine rein photopische Natur auf. Das beweisen Untersuchungen von Dodt (1962), Mahnecke (1957), Burian & Sipey (1959), Sverák & Peregrin (1960) und Elenius (1969).

Diese Besonderheit der zweiten Antwort (A_2) ist nicht durch eine passive Refraktärphase infolge der photochemischen Reaktionen nach der Erstbelichtung, sondern vielmehr als eine aktive postexcitatorische Hemmung des Stäbchensystems zu erklären (Granit 1937, Dodt 1952, Elenius 1969). Für diesen Hemmungsvorgang sind eher neuronale Verbindungen verantwortlich zu machen als die Metaboliten des photochemischen Abbaues des Rhodopsins. Sie dürften mit den nervösen Schaltvorgängen in den Anfangsphasen der Dunkeladaptation verwandt sein, die den photochemischen Prozessen vorangehen und psychophysisch von Crawford (1947) ebenso wie von Baker (1963) nachgewiesen wurden. Die wichtigsten elektrophysiologischen Arbeiten hierzu wurden von Granit (1947) geleistet; neuere, subtilere Beweise stammen von Dowling und seiner Arbeitsgruppe (1963, 1970).

1.1 Eigene Untersuchungen

1.1.1 Methodik Die technischen Parameter bei den Ableitungen gleichen denen die 1970 eingehend beschrieben wurden. In Anlehnung an Elenius (1969) wurden die Doppelblitz-Stimuli mit konstanter Reizintensität (2 Ws), konstantem Intervall zwischen den Einzelblitzen (120 ms) und konstanter Reizfolgezeit (5000 ms) zwischen den Blitzpaaren ausgelöst. Zunächst wurde das Doppelblitz-ERG an 9, augengesunden Probanden im Alter von 20 bis 30 Jahren registriert. An Hand der Ergebnisse von 43 Augen prüften wir das Verhalten der zweiten Antwort im Verlaufe der Dunkeladaptation bei 16 Augen im Verlaufe der Helladaptation und bei 10 Augen im Verlaufe der Helladaptation nach Rotlicht-Reizen. Während eines 24 min dauernden Tests wurden jeweils nach 4 Minuten drei Doppelblitz-Reize ausgelöst.

1.1.2 Ergebnisse Die Untersuchungsergebnisse, die in Abb. 1 zusammengefasst sind, zeigen, dass

- während der Dunkelanpassungsperiode die erste Antwort (A_{1D}) ansteigt (abnehmende ERG-Schwelle bei zunehmender Stäbchenaktivität), die zweite Antwort (A_{2D}) dagegen abfällt (ansteigende Reizschwelle der Zapfen bei zunehmender Dunkelanpassung)
- im helladaptierten Zustand die 1. Antwort (A_{1H}) und die 2. Antwort (A_{2H}) gleich gross sind und sich während der Untersuchungszeit nicht verändern

- im helladaptierten Zustand und bei Rotlichtreizung beide Antworten (A_{1R} und A_{2R}) ebenfalls photopischer Natur sind unverändert bleiben und hierbei die zweite etwas grösser ist als die erste

Wir entnehmen daraus eine Bestätigung der oben dargestellten Auffassung über die Natur der beiden Antworten im DB ERG. Wir halten dieses für geeignet um Teilprozesse der vielfältigen Interaktionen zwischen photopischem und skotopischem System der Netzhaut zu untersuchen.

Das DB ERG der diabetischen Retinopathie

2.1 Krankengut und Methodik

103 diabetische Patienten (905 Augen) des Zentralinstituts für Diabetes in Karlsburg (Direktor Prof. Dr. Bibergeil) wurden untersucht.

Die Retinopathiestadien verteilen sich wie folgt:

Stadium	Befunde	Anzahl der Augen
0	keine ophthalmoskopisch sichtbaren Veränderungen	21
I	Mikroaneurysmen Sanguinationen	16
II	Mikroaneurysmen Sanguinationen harte und Cotton wool Exsudate	54
III	alle Formen der Proliferation bis zur Traktionsamotio	114
		<hr/> 205

Stadium I und II wurden für einzelne Darstellungen zusammengefasst und als Retinopathia simplex der Retinopathia proliferativa gegenübergestellt.

In Anlehnung an Elsenus wurde folgende Reizmethodik benutzt: konstante Intensität ($> W_2$) konstantes Intervall (10 ms) zwischen den Einzelblitzen und variable Reizfolgezeit (350 400 500 800 1000 1 000 2000 3000 4000 und 5000 ms) zwischen den Blitzpaaren. Aus der b-Welle der ersten Antwort (A_1) und der zweiten Antwort (A_2) des DB ERG bildeten wir den Quotienten

$$\frac{A_1 - A_2}{A_1}$$

Die Werte des dimensionslosen Quotienten sind aufgetragen gegen die Reizfolgezeit als Quotientenverlaufskurven dargestellt.

Neben den Diabetikern wurden 35 augen- und stoffwechselgesunde Probanden untersucht, um deren Ergebnis mit den pathologischen Befunden gegenüberstellen zu können.

2 Ergebnisse

Die getrennte Darstellung der beiden Antworten (Abb. 2) zeigt, dass sich A_1 bei den einfachen und proliferativen Retinopathieformen nicht stark von der Normgruppe unterscheidet und innerhalb ihrer Standardabweichung liegt. Die zweite b-Welle (A_2) wird dagegen viel stärker beeinträchtigt. Sie liegt bei den Retinopathiestadien unterhalb der Normwerte und an deren unterer Standardabweichung.

Besonders deutlich ist die Differenz der Reizantworten zwischen den Intervallen von 400 bis 3000 ms. Die Quotientenverlaufskurve (Abb. 3) ist umso höher, je fortgeschrittener die diabetischen Netzhautveränderungen sind. Die Werte für die Retinopathia proliferativa (R III) befinden sich ausserhalb der oberen Standardabweichung. Diese Erhöhung des Quotienten wird durch die erniedrigte Amplitude von A_2 bedingt und zeigt ein pathologisches Ergebnis an.

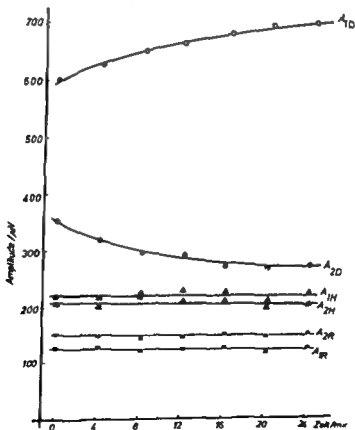


Abb. 1

Verhalten der 1. Antwort (A_1) und der 2. Antwort (A_2) bei Dunkeladaptation (D), Helladaptation (H) und Rotlichtreizung (R) im Doppelblitz LRG

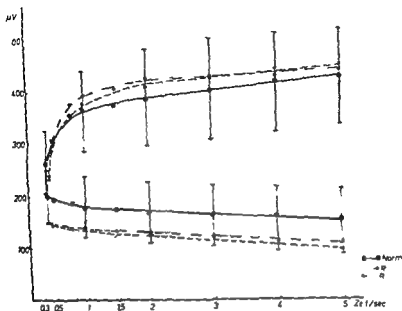


Abb 2

Amplitudenverlaufskurve der 1. Antwort (A_1 , obere Kurve) für die Retinopathia simplex (R) und Retinopathia proliferativa (R_p) verglichen mit Normwerten. Der untere Kurvenverlauf stellt die 2. Antwort (A_2) dar.

Bildet man für die Quotienten einer jeden Doppelblitzreizung im Untersuchungsgang ein Gesamtmittel (Abb 4) oder verwendet man die Quotienten der Blitzfolgezeit 2000 und 5000 ms, so wird der Unterschied zwischen den Patientengruppen noch deutlicher und lässt sich mit Hilfe des χ^2 Testes statistisch sichern ($P = 0,01\%$ signifikant).

Eine grosse Zahl von Verlaufskontrollen mit dem DB ERG während der Entwicklung der diabetischen Retinopathie überzeugte uns, dass diese Methode von klinischem Wert sein kann und Verschlechterungs- oder Besserungsphasen auszudrücken vermag. Um verbindlich hierzu Stellung nehmen zu können, halten wir aber weitere Untersuchungen für erforderlich. Hier sei das lediglich an Ergebnissen zum Ausdruck gebracht, die wir bei 41 Augen vor und nach der Lichtkoagulation registrieren konnten. Bei 33 Augen ($\sim 81\%$) konnten wir als Zeichen der Besserung eine Senkung des Quotienten beobachten, die durch eine Erhöhung von 1 zustande kam. Bei 8 Augen verschlechterte sich der Quotient. Überraschend für uns war, dass dieses elektroretinographische Ergebnis stets dem ophthalmoskopisch erhobenen Befund entsprach (Abb 5).

2.2 Ergebnisse

Die getrennte Darstellung der beiden Antworten (Abb 2) zeigt dass sich A_1 bei den einfachen und proliferativen Retinopathieförmungen nicht stark von der Normgruppe unterscheidet und innerhalb ihrer Standardabweichung liegt Die zweite h Welle (A_2) wird dagegen viel stärker beeinträchtigt Sie liegt bei den Retinopathiestadien unterhalb der Normwerte und an deren unterer Standardabweichung

Besonders deutlich ist die Differenz der Reizantworten zwischen den Intervallen von 400 bis 3000 ms Die Quotientenverlaufskurve (Abb 3) ist umso höher je fortgeschrittener die diabetischen Netzhautveränderungen sind Die Werte für die Retinopathia proliferativa (R III) befinden sich ausserhalb der oberen Standardabweichung Diese Erhöhung des Quotienten wird durch die erniedrigte Amplitude von A_2 bedingt und zeigt ein pathologisches Ergebnis an

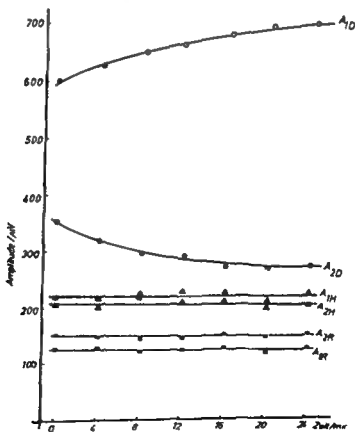


Abb 1

Verhalten der 1. Antwort (A_1) und der 2. Antwort (A_2) bei Dunkeladaptation (D), Helladaptation (H) und Rotlichtreizung (R) im Doppelblitz I RC

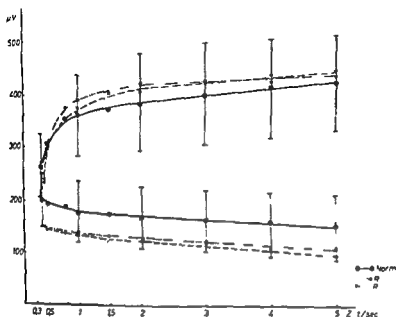


Abb. 7

Amplitudenverlaufskurve der 1. Antwort (A_1 , obere Kurve) für die Retinopathia simplex (R_1) und Retinopathia proliferativa (R_2) verglichen mit Normwerten. Der untere Kurvenverlauf stellt die 2. Antwort (A_2) dar.

Bildet man für die Quotienten einer jeden Doppelblitzreizung im Unternehmungsgang ein Gesamtmittel (Abb. 4) oder verwendet man die Quotienten der Blitzfolgezeit 2000 und 5000 ms, so wird der Unterschied zwischen den Patientengruppen noch deutlicher und lässt sich mit Hilfe des t-Testes statistisch sichern ($P = 0.01\%$ signifikant).

Eine grosse Zahl von Verlaufskontrollen mit dem DB-ERG während der Entwicklung der diabetischen Retinopathie überzeugte uns, dass diese Methode von klinischem Wert sein kann und Verschlechterungs- oder Besserungsphasen auszudrücken vermag. Um verbindlich hierzu Stellung nehmen zu können, halten wir aber weitere Untersuchungen für erforderlich. Hier sei das lediglich an Ergebnissen zum Ausdruck gebracht, die wir bei 41 Augen vor und nach der Lichtkoagulation registrieren konnten. Bei 33 Augen (= 81%) konnten wir als Zeichen der Besserung eine Senkung des Quotienten beobachten, die durch eine Erhöhung von A zustande kam. Bei 8 Augen verschlechterte sich der Quotient. Überraschend für uns war, dass dieses elektroretinographische Ergebnis stets dem ophthalmoskopisch erhobenen Befund entsprach (Abb. 5).

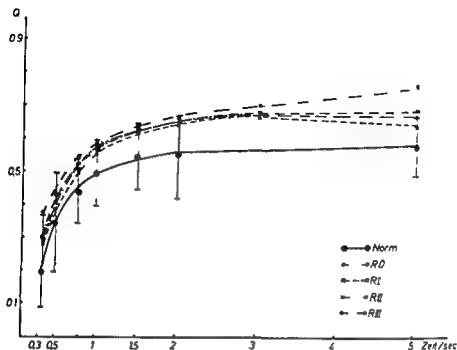


Abb 3

Mittlere Quotientenverlaufskurve der einzelnen Retinopathiestadien Erhöhung des Quotienten = pathologischer Ausfall

Diskussion

Ähnlich wie durch das Verhalten des oszillatorischen Potentials kann auch mit Hilfe des Doppelblitz Elektroretinogrammes die Beeinträchtigung der bioelektrischen Potentialbildung in der Netzhaut durch die diabetische Retinopathie nachgewiesen werden. Da das auch für die Untersuchung einzelner Patienten zutrifft, knüpfen sich hieran klinisch diagnostische Erwartungen. Die sich immer deutlicher abzeichnenden Möglichkeiten einer therapeutischen Beeinflussung der Erkrankung erhöhen das Bedürfnis, ihren phasenhaften Verlauf mit objektiven Verfahren erfassen zu können. Die Netzhäute diabetischer Patienten reagieren auf zwei kurze Lichtreize von 2 Ws, die im Abstand von 120 ms aufeinander folgen und die beide während der Untersuchung in einer immer länger wahrenden Dunkelanpassungszeit dargeboten werden, in charakteristischer Form. Während die erste Antwort mit vorwiegend skotopischem Charakter nicht von der Norm abweicht, ist die zweite Antwort durch photopische

Eigenschaften charakterisiert und deutlich erniedrigt. In dimensionsloses Verhältnis beider Antworten, das durch den Quotienten

$$\frac{A_1 - A_2}{A_1}$$

gebildet wird, weicht bei längerer Dunkeladaptationszeit stärker von der Norm ab als bei kurzer. Der Mittelwert dieser Quotienten unterscheidet sich mit einer für elektroretinographische Ergebnisse gewöhnlichen Streubreite bereits bei Diabetikern ohne ophthalmoskopisch sichtbare Retinopathie statistisch gesichert von der Gruppe Augengesunder und steigt in pathologischer Weise an, wenn der Gefassschaden ophthalmoskopisch sichtbar wird.

Mit der weiteren Entwicklung der Retinopathie wird dieses Verhalten noch deutlicher. Zwischen der einfachen und der proliferativen Retinopathie bestehen gesicherte Differenzen. Hierbei muss hervorgehoben werden, dass bei

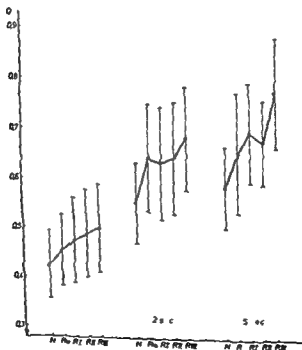


Abb. 3

Gesamtziel der Quotienten einer jeden Doppelblitzreizung und der Quotienten der Blitzfolge zu 2 und 5 sec

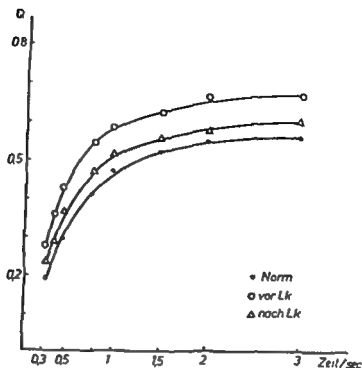


Abb. 1

Quotientenverlaufskurve vor und nach Lichtkoagulation (Lk) verglichen mit Normwerten. Nach Lichtkoagulation ist die deutliche Erniedrigung des Quotienten Ausdruck einer verbesserten Netzhautfunktion.

dieser Studie in der Gruppe R III überwiegend beginnende Gefäßproliferationen (etwa Stadium I nach Davis) zusammengefasst sind.

Die diabetische Retinopathie fassen wir als Kausalkette auf, die aus folgenden Gliedern besteht:

- Pathologischer Umbau der retinalen Endstrombahn als Folge der allgemein auftretenden diabetischen Mikroangiopathie
- Störung der retinalen Mikrozirkulation und
- funktionelle Verluste in den Ganglien und synaptischen Verbindungen der inneren Netzhautschichten, die dadurch verursacht werden.

Es ist gegenwärtig noch sehr schwer, diese letzteren frühzeitig nachzuweisen. Die gebräuchlichen psychophysischen Untersuchungsmethoden (Visus, Gesichtsfeld) bieten erst dann pathologische Ergebnisse, wenn die Retinopathie weit fortgeschritten ist und die betroffenen Strukturen irreversibel geschädigt sind. Sie sind daher auch wenig zur Frühdiagnostik oder zu Kontrollunter-

suchungen geeignet. Die elektrodiagnostischen Verfahren bieten allein die Möglichkeit funktionelle Vorgänge in den inneren Netzhautschichten zu beurteilen, weil unsere Kenntnisse über die retinale Organisation durch mehrere Arbeitsgruppen mit Hilfe einer subtilen elektrophysiologischen Methodik wesentlich erweitert wurden (zusammengefasst bei Dowling 1970).

Dass eine Erkrankung im Ausbreitungsgebiet der Arteria centralis retinae in einer elektroretinographischen Untersuchungsmethode ihren Niederschlag findet, die auf dem photopisch skotopischen funktionellen Dualismus der Netzhaut basiert, erscheint weniger verwunderlich, da die Bedeutung integrierender neuronaler Schaltvorgänge bei allen Adaptationsabläufen allgemein anerkannt ist. Die stärkere Einschränkung der Antworten des photopischen Systems bei der diabetischen Retinopathie, die auch im Erlöschen des oszillatorischen Potentials zum Ausdruck kommt, kann allerdings zum gegenwärtigen Zeitpunkt nur in hypothetischer Form erklärt werden. Zunächst wird mit der bevorzugten Ausbreitung der diabetischen Retinopathie am hinteren Iunduspol ein Areal getroffen, in dem die Anzahl der Zapfen überwiegt. Möglicherweise sind deren synaptische und ganglionäre Verbindungen gegenüber mikrozirkulatorischen Dekompensationen anfälliger als die anderen Rezeptoren. Zudem erscheint es denkbar, dass die wesentlich grosseren rezeptiven Felder, die unter ausgedehnten konvergierenden synaptischen Verbindungen einer grossen Ganglienzelle unter skotopischen Bedingungen zugeordnet sind, durch umschriebene hypoxische Areale weniger gestört werden.

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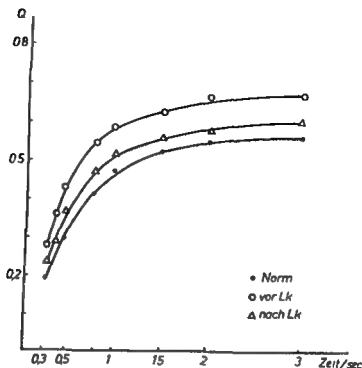


Abb 5

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ON THE OSCILLATORY POTENTIALS OF THE HUMAN ELECTRORETINOGRAM IN LIGHT AND DARK ADAPTATION

III Thresholds and relation to stimulus intensity on adaptation to background light

BY

L. WACHTMEISTER

The thresholds and the relation to stimulus intensity of the oscillatory potentials and the slow potentials (a- and b-wave) of the human ERG were studied on adaptation to a steady background of different intensities. The total energy and dominant frequency of the oscillatory potentials were calculated by a combined impulse response and Fourier analysis when different intensity of stimulus light was used on adaptation to a maximal background illumination (about 1.5×10^3 photopic cd/m²).

The curve of incremental thresholds of the oscillatory potentials shows a flat range on exposure to background light below 1 cd/m² (the level of adaptation at which the Purkinje shift of the b-wave occurs) before rising along a linear section. The sensitivity of the oscillatory potentials declines on adaptation to bright background illumination when the sensitivity of the cones is higher than that of the rods.

The linear section of $\log \Delta I$ (incremental threshold) vs $\log I$ (background light) does not obey the Weber-Fechner law [$\log \Delta I = k \log (I + I_D)$] but will approach Barlow's square root formula [$\log \Delta I = k \log (I + I_0)^{1/2}$] and the line has a slope of 0.33. There is, as expected, no sign of saturation in the rapid decrease in sensitivity of the oscillatory potentials on adaptation to the brightest background illumination used.

Oscillatory potentials recorded just at threshold have a high frequency (about 160 Hz) but the frequency decreases (to around 10 Hz) with

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The curve of incremental thresholds of the oscillatory potentials shows a flat range on exposure to background light below 1 cd/m (the level of adaptation at which the Purkinje shift of the b wave occurs) before rising along a linear section. The sensitivity of the oscillatory potentials declines on adaptation to bright background illumination when the sensitivity of the cones is higher than that of the rods.

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Oscillatory potentials recorded just at threshold have a high frequency (about 160 Hz) but the frequency decreases (to around 100 Hz) with

stronger stimuli on adaptation to maximal background illumination. The stimulus response curve appears linear in weak background illumination but changes to a plateau at the background intensity at which the Purkinje shift of the b wave occurs (about 1 cd/m²). Thus prominent cone activity as such does not seem to be able to grade the oscillatory potentials.

The incremental threshold curve of the oscillatory potentials was similar to that of the a wave but differed from that of the b wave.

The slow potentials (a and b wave) act independently of the oscillatory potentials in response to stimulus of different intensities supporting the view that the origin of the oscillatory potentials is quite separate from that of the a and b wave.

Key words electroretinography – oscillatory potentials – light and dark adaptation – Fourier analysis – thresholds – relation to stimulus intensity – background illumination

Throughout history of research of electroretinography there has been an attempt by many authors to correlate the electrical response of retina to the state of adaptation under which it has been recorded.

Already Kühne & Steiner (1880) found that light adaptation reduced the magnitude of the electrical response of retina on light stimulation: the electroretinogram (ERG). Biersdorf & Armington (1960) showed that increasing levels of light adaptation produce decreases in the amplitude of the positive and negative components (a, b and x waves) of the ERG. They demonstrated that long latency components are affected by lower levels of light adaptation and to greater extent than short latency components.

The oscillatory potentials of the human ERG also decreased on light adaptation provided they were recorded under optimal conditions in dark adaptation. On the other hand there was an increase of the oscillatory energy in low background illumination in comparison with the wavelets recorded under sub-optimal conditions in the dark (Algvere & Wachtmeister 1972).

When studying the electroretinographic and sensory threshold of sensitivity of the human eye van Lith (1966) showed that the brightness required for a criterion voltage of 35 μ V of b or x wave is about 10³ times that for the visual sensory threshold. The electrical thresholds (incremental thresholds) are essentially unaltered within a range of about 3 log units above the psychophysical absolute threshold (Biersdorf, Grand & Lawson 1966; van Lith 1966). Above this range electrical thresholds are similar to psychophysical thresholds as a function of colour and duration. Thresholds rise according to Weber's law: Δc the increment in threshold (ΔI) is linearly proportional to the increase of

adapting luminance (1) with a slope of the line being 1.0 (Biersdorf Granda & Lawson 1963 Dowling 1967). The corresponding part of the threshold curve of the a wave of the ERG shows a slope close to 0.6 (Biersdorf Granda & Lawson 1966). For the cone retina (squirrel) the increment threshold is found to be small for all test light (Dodt 1962).

No systemic study has been published regarding thresholds and relation to stimulus intensity of the oscillatory potentials of the human ERG on adaptation to steady backgrounds. The aim of this report is to provide data regarding the behaviour of the oscillatory potentials in this respect. In addition the amplitude, latency and frequency of the oscillatory potentials are studied under pure photopic conditions and estimated by means of a mathematical evaluation using a combined impulse response and Fourier analysis (Algvere & Westbeck 1972).

Apparatus and Methods

The set for recording the ERG was the same as previously used and described (Algvere & Wachtmeister 1972). The maximum luminance of the light stimulus was about 1×10^4 photopic cd/m². Its colour temperature corresponded to about 6500 K. The luminance flux attained a maximum in less than 2 msec and then decreased exponentially. During about 25 msec (from 0.9 msec to 9.4 msec from the onset of light stimulus) 75% of its maximal luminous intensity was maintained. The adapting light had a maximum luminance of about 1.5×10^4 photopic cd/m² (corresponding to about 4.1×10^3 scotopic cd/m²). Its colour temperature was about 3150°K.

The same electronic equipment, calibration and band pass of the recording system were used as described previously (Algvere & Wachtmeister 1972). A contact lens according to Lawwill Burian (1966) with the reference electrode as a part of the contact lens was used. The ground electrode was placed on the ear lobe. The electric signal was amplified and displayed on a double beam cathode ray oscilloscope (Solartron C\ 1442 3 or Hewlett Packard 132 A) and photographed.

Methods III measurements

Amplitudes and peak latencies of the a wave, b wave and oscillatory potentials were measured as previously described (Algvere, Wachtmeister & Westbeck 1972).

In one series of experiments the energy and dominant frequency of the oscillatory potentials were analysed with a combined impulse and Fourier

analysis as described in a previous work (Algvare & Westbeck 1972) The ERG's shown in the pictures were all recorded from the left eye of the same subject and evaluated by calliper square and magnifier measurements as well as by Fourier analysis

Procedures

Investigations were made in two young and healthy persons (one woman and one man) Central visual acuity visual sensitivity visual fields colour vision and the fundus were all carefully examined and found to be normal The pupil was dilated with Mydracyl® (Alcon lab) to more than 6 mm in diameter Surface anesthesia of the eye was established with a few drops of Novesin® (Wander) The fellow eye was occluded

The following two procedures were performed

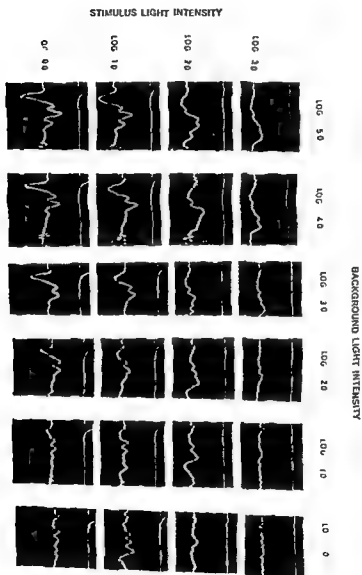
I The threshold of the ERG was studied on adaptation to background illumination of different intensities A series of three flashes of the same intensity was given After these three flashes the intensity of the next series of three flashes was increased at a logarithmic scale There was an interval of 30 seconds between each flash even though the intensity of each series of three flashes varied over a range of 7 log units The light adaptation caused by one series of three flashes did not have any significant effect on the ERG in response to the second or third flash in the consecutive series The procedure was repeated with background light intensities varying over a range of 5 log units The slow potentials were recorded with a low sweep speed and low amplification (0.2 mV/cm 20 msec/cm) in response to the second or third flash respectively The oscillatory potentials were displayed with high sweep speed and high amplification (0.1 mV/cm 10 msec/cm) in response to the second or third flash respectively On the Hewlett Packard oscilloscope the upper cathode ray beam presented the slow potentials and the lower beam displayed the oscillatory potentials simultaneously

II The dependence of the ERG on the light stimulus intensity was studied as adapted to background illumination of different intensities The stimulus

Fig 1

Threshold and relation to stimulus light intensity of the oscillatory potentials on adaptation to background light of different intensities The background light was varied over a range of 5 log units A series of three flashes of the same intensity was given The oscillatory potentials and the slow potentials were recorded alternating in response to the second and the third stimulus flash The intensity of all three flashes increased in a logarithmic scale There was 30 sec between each flash although the intensity of the flashes varied

Oscillatory Potentials of Human ERG



flashes were given as in the previous procedure and varied over a range of 7 log units. There was an interval of 30 seconds between each series of three flashes. The background illumination varied over a range of 5 log units.

Results

The threshold of the ERG was recorded on adaptation to background light of different intensities varying from $\log I_B = -5.0$ to $\log I_B = 0$ (Fig. 1). Three consecutive flashes of the same intensity were given at an interval of 30 sec and the ERG was recorded in response to the second and third (stimulus) flash. The intensity of all three flashes was varied from $\log I_s = -4.0$ to $\log I_s = 0$.

1A. ERG THRESHOLDS

The oscillatory potentials were recorded at stimulus intensity of about $\log I_s = -3.0$ (Fig. 1) on adaptation to the weakest background illumination. On adaptation to maximal background light intensity ($\log I_B = 0$) the oscillatory potentials were not distinguished until stimulus intensity of about $\log I_s = -2.0$ and were distinctly visible at stimulus intensity of $\log I_s = -1.3$. The ERG recorded in response to the stimulus intensity of $\log I_s = -1.0$ on adaptation to background light of $\log I_B = 0$ and with stimulus intensity of $\log I_s = -2.0$ on exposure to background illumination of $\log I_B = -1$ and $\log I_B = -2.0$ (Fig. 1) was similar to that which shows interference between the on and off effect (cf. Nagata 1962).

A wave of about 40 μV was recorded at stimulus intensity of $\log I_s = -3.3$ on adaptation to the weakest background light ($\log I_B = -5.0$) (Fig. 2). A distinct wave was not recordable until the stimulus intensity was $I_s = -2.3$ on adaptation to maximal background illumination ($\log I_B = 0$).

The a wave was double peaked, the second trough (a) being the largest in response to stimulus light intensity of $\log I_s = -2.0$ or weaker on adaptation to weak background illumination ($\log I_B = -5.0$ and -4.0).

At the weakest background illumination used ($\log I_B = -5.0$) a scotopic b wave of about 30 μV appeared at stimulus intensity of $\log I_s = -6.0$ (Fig. 2). A photopic b wave appeared at $\log I_s = -4.0$. The peak latencies were 104 and 62 msec respectively. In maximal background illumination ($\log I_B = 0$)

Oscillatory Potentials of Human ERG

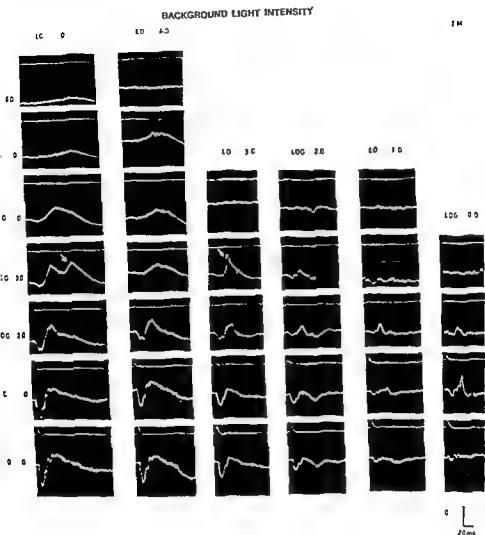


Fig 9

Threshold and relation to stimulus light intensity of the amplitude of the a and b wave on adaptation to background light of different intensities. The procedure was the same as in Fig 1. In the ERGs recorded in response to stimulus light intensities of $\log I = -6.0$ up to $\log I = -4.0$ and in the ERGs recorded during maximal background light intensity ($\log I_B = 0$) the vertical calibration represents $100 \mu V$. The ERG response recorded in background light of $\log I_B = -3.0$ and $\log I_B = -2.0$ and with stimulus light of $\log I = 3.0$ have an artefact indicated by an arrow.

flashes were given as in the previous procedure and varied over a range of 7 log units. There was an interval of 30 seconds between each series of three flashes. The background illumination varied over a range of 5 log units.

Results

The threshold of the ERG was recorded on adaptation to background light of different intensities varying from $\log I_B = -5.0$ to $\log I_B = 0$ (Fig. 1). Three consecutive flashes of the same intensity were given at an interval of 30 sec and the ERG was recorded in response to the second and third (stimulus) flash. The intensity of all three flashes was varied from $\log I = -4.0$ to $\log I_s = 0$.

1A ERG THRESHOLDS

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An a wave of about 40 μV was recorded at stimulus intensity of $\log I = -3.3$ on adaptation to the weakest background light ($\log I_B = -5.0$) (Fig. 2). A distinct a wave was not recordable until the stimulus intensity was $I = -2.3$ on adaptation to maximal background illumination ($\log I_B = 0$).

The b wave was double peaked, the second trough (a) being the largest in response to stimulus light intensity of $\log I = -2.0$ or weaker on adaptation to weak background illumination ($\log I_B = -5.0$ and -4.0).

At the weakest background illumination used ($\log I_B = -5.0$) a scotopic b wave of about 30 μV appeared at stimulus intensity of $\log I_s = -6.0$ (Fig. 2). A photopic b wave appeared at $\log I = -4.0$. The peak latencies were 104 and 62 msec respectively. In maximal background illumination ($\log I_B = 0$)

tion) electrical response at different adaptation illuminities (I) The criterion voltage of the slow potentials was $33 \mu\text{V}$ A criterion response of 2.5 arbitrary units was used for the oscillatory potentials

The curve of the incremental threshold (2.5 arbitrary units) of the oscillatory potentials remained fairly constant up to a background illumination of $\log I_B = -3.0$ (Fig. 3) Thereafter there was a slow rising portion of the incremental threshold function The slope of this function was about 0.33

The threshold ($33 \mu\text{V}$) of the a wave remained rather low up to a background illumination of $\log I_B = -2.0$ (Fig. 3) At adaptation of $\log I_B = -2.0$ and above the threshold curve appeared to be a linear function the slope of which was calculated to be about 0.66

The curve of the incremental threshold ($33 \mu\text{V}$) of the b wave rose with a fairly constant slope of about 0.73 within the range of adaptation levels examined (Fig. 3) The lowest of the adaptation levels ($\log I_B = -5.0$) was about 3-4 log units above the absolute threshold ($\log I = -8.0$)

Evidently there was a difference in the slope of the function of incremental threshold of the a wave b wave and oscillatory potentials (Fig. 3) There was an immediate rise of the b wave function whereas that of the a wave and the oscillatory potentials started at levels of adaptation which were three and four log units brighter respectively The slope of the b wave curve was somewhat steeper than that of the a wave which was steeper than that of the oscillatory potentials

II RELATION TO STIMULUS LIGHT INTENSITY

During adaptation to low background illumination ($\log I_B = -5.0$ and -4.0) the summed amplitude of the oscillatory potentials increased as the stimulus intensity augmented (Fig. 4) When stronger background light intensities ($\log I_B = -1.0$ to 0) were used there were smaller increments in the oscillatory potentials when the stimulus intensity was increased The oscillatory potentials gained in amplitude over a range of one log unit of stimulus light intensity Above that range there seemed to be no further increase as the stimulus intensity augmented

On adaptation to maximal background illumination the energy of the oscillatory potentials was low and did not show any significant change as stimulus light intensity increased (Fig. 5) The dominant frequency decreased from about 100 Hz to about 125 Hz as the stimulus light intensity increased (Fig. 6) which was also shown as an increase of about 6 msec of the interval between the first and the last oscillatory potential (0_1-0_1) shown in Fig. 7

the b wave (photopic) was not recordable until stimulus intensity of $\log I_s = -2.3$

The ERG recorded in response to stimulus intensity of $\log I_s = -1.0$ on adaptation to maximal background illumination ($\log I_B = 0$) (Fig. 2) resembled that which shows interference between on and off effect (cf. Best & Bohnen 1957; Nagata 1962).

Consequently the threshold of the oscillatory potentials the a wave and the photopic b wave increased about 1 log unit when the background light increased from minimum ($\log I_B = -5.0$) to maximum ($\log I_B = 0$) (Figs. 1 and 2). There was no significant change of the thresholds recorded in the weakest background illumination compared to thresholds in dark adaptation (cf. Algerey, Wachtmeister & Westbeck 1972).

1. INCREMENTAL THRESHOLDS

In the present electroretinal study on the sensitivity of the eye at various adaptation levels the incremental threshold (ΔI) was measured. The incremental threshold expresses the increase in threshold (or decrease in sensitivity) per increase in the intensity of light stimulus necessary to elicit a constant (cri-

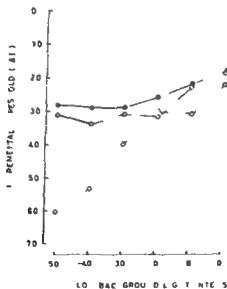


Fig. 3

Incremental threshold (differential threshold) of the oscillatory potentials the a and b wave on adaptation to background light of different intensities. The procedure was the same as in Fig. 1. The incremental threshold (ΔI) is plotted against background light intensity on the X-axis. Black circles oscillatory potentials. Open circles continuous line a wave. Open circles dashed line b wave.

Oscillatory Potentials of Human ERG

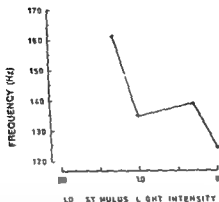


Fig 6

Dominant frequency of the oscillatory potentials on adaptation to background light of maximal intensity ($\log I_B = 0$). The procedure was the same as in Fig 1. Frequency of the oscillatory potentials plotted against stimulus light intensity.

The amplitude of the a wave showed even increments within a range of 4 log units as the stimulus intensity increased (Fig 8). This uniform increase was progressively less prominent as the background illumination increased. On adaptation to maximal background illumination there was a very slight but

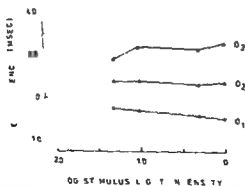


Fig 7

Peak latencies of the individual oscillatory peak (O_1 , O_2 , O_3) on adaptation to background light of maximal intensity ($\log I_B = 0$) from ERGs shown in Fig 1. The procedure was the same as in Fig 1. Peak latencies plotted against stimulus light intensity. The average error of repetitive calliper square readings was less than 0.5 msec.

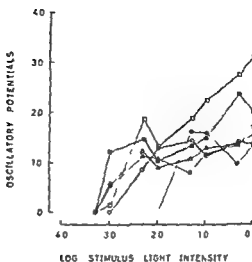


Fig 4

Oscillatory potentials (summed amplitude of individual oscillatory peaks) in relation to stimulus light intensity on adaptation to background light of different intensities. The procedure was the same as in Fig 1. The oscillatory potentials were measured in arbitrary units (mm) and plotted against stimulus light intensity of the second or third stimulus flash eliciting the ERG's shown in Fig 1. The calibration used was 0.1 mV/10 msec/cm. The symbols used represent the following intensities of background light: white squares ($\log I_B = -5.0$), black squares ($\log I_B = -4.0$), white triangles ($\log I_B = -3.0$), black triangles ($\log I_B = -2.0$), white circles ($\log I_B = -1.0$), black circles ($\log I_B = 0$).

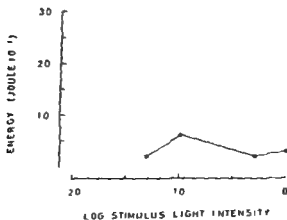


Fig 5

Calculated energy of the oscillatory potentials on adaptation to background light of maximal intensity ($\log I_B = 0$). The procedure was the same as in Fig 1. Energy of the oscillatory potentials plotted against stimulus light intensity.

up to a maximum beyond which it declined (Fig 9) On adaptation to background light of low intensity ($\log I_B = -5.0$) the maximum amplitude was attained at a stimulus intensity of about $\log I = -3.0$ At more intense background illumination ($\log I_B = 0$) the maximum was attained at higher stimulus intensity (about $\log I = -1.0$) This behaviour of the a wave and b wave is in agreement with the findings of Elenius & Ahlström (1961) and Auerbach (1967) although their recording and procedure were different

Consequently the oscillatory potentials and the a wave showed about the same relationship to stimulus intensity although the form of the stimulus response curve was not exactly the same when low background illumination was used There was a less increase of the amplitude of the a wave as the background light intensity increased In strong light adaptation there was only a very slight if any increase of the oscillatory potentials The amplitude of the b wave on the other hand showed an increase up to a maximum which was attained at a higher stimulus intensity as the background light intensity increased

DISCUSSION

The present results show that the sensitivity (the reciprocity of ΔI) of the b wave changes over a wide range (4 log units) whereas the sensitivity of both the a wave and the oscillatory potentials varies only within 1 log unit on adaptation to background light of different intensities used in this study

The curve of incremental threshold of the a wave and the oscillatory potentials shows a flat range before rising along a linear section on exposure to a brighter background light (above $\log I_B = -3.0$ to -2.0 in this study) At this level of adaptation (corresponding to about 1–10 cd/m²) which bleaches a negligible amount of photopigments (Rushion 1954–59 1963 1965 1966) the spectral sensitivity of the b wave of the human ERG changes from scotopic to photopic dominance (van Lith 1966 Biersdorf Granda & Lawson 1966) Thus the threshold of the a wave and the oscillatory potentials remains low when rod sensation predominates (immediately above cone threshold) but rises continuously when the sensitivity of the cones is higher than that of the rods and during intense bleaching when only cone response is apparent ($\log I_B = -1.0$ and 0) (Mandelbaum & Nelson 1960) The sensitivity of the oscillatory potentials declines on adaptation to bright background light ($\log I_B = -3.0$ to 0) when the sensitivity of the cones is higher than that of the rods This indicates that the oscillatory potentials are most easily elicited when the retina is organized in a pattern where the rods are still more sensitive than the cones

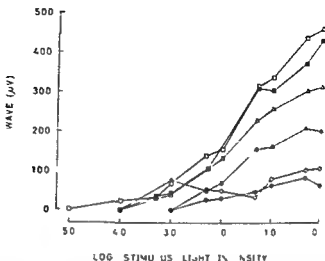


Fig 8

Amplitude of the a wave in relation to stimulus light intensity on adaptation to background light of different intensities. The procedure was the same as in Fig 1. The amplitude of the a wave plotted against stimulus light intensity of the second or third stimulus flash eliciting the ERGs shown in Fig 2. The same symbols are used as in Fig 4.

still nearly linear increase of the a wave within a range of 3 log units as stimulus intensity augmented.

The amplitude of the b wave increased with the rise in stimulus intensity.

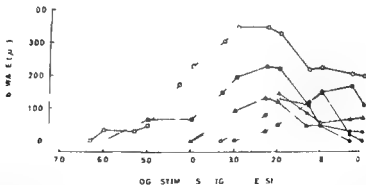


Fig 9

Amplitude of the b wave in relation to stimulus light intensity on adaptation to background light of different intensities. The procedure was the same as in Fig 1. The amplitude of the b wave was plotted against the intensity of the second or third stimulus flash eliciting the ERGs shown in Fig 2. The same symbols are used as in Fig 4.

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The a-wave giving some information of the receptor cell activity shows a significant but limited degree of adaptation in the human eye. This may be accounted for by a mechanism of response compression modified by effects of photopigment bleaching suggested by Boynton & Whitten (1970) in an experimental study of the LRP (late receptor potential) of monkey's ERG. Since no inhibitory feed back from proximal retinal neurons to receptor cells seems to exist a part of the adaptive machinery will take place in the cones themselves (Boynton & Whitten 1970).

The linear section of the curve of $\log \Delta I$ (incremental threshold) vs $\log I$ (background light intensity) for the b-wave does not obey Weber-Fechner's law [$\log \Delta I = k \log (I + I_D)$] but has a shallower slope. The corresponding function for the a-wave and the oscillatory potentials have slopes even less steep than that for the b-wave. Incremental curves of the a-wave and the oscillatory potentials seem to approach Barlow's square root formula [$\log \Delta I = k \log (I + I_D)^{1/2}$] and may reflect a change in temporal summation of the response. Barlow (1957, 1958) assumes from his psychophysical data the presence of intrinsic noise (dark light I_D) equivalent to a constant dim illumination of the retina in addition to the light actually stimulating the eye. This noise of the visual system is considered to result from a maintained activity in the receptors probably due to spontaneous decomposition of photopigments. Also the elevation of threshold associated with bleaching is considered due to a spurious disturbance or "noise" generated in the receptors (Barlow & Sparrock 1964, Alpern & Rushton 1967). Boynton & Whitten (1970) on the other hand suggest a compression of response for cone receptor potentials simply depending upon intensity required to drive the response to a criterion voltage.

A change in spatial organization has also been proposed as a mechanism of the change in Weber-Fechner's law. Alpern, Rushton & Torri (1970a) demonstrated that all their psychophysical observations showed alternation of an inhibitory signal (N) in proportion to $(I + I_D)$. This function fits the Weber-Fechner threshold relation even though it may be a great simplification of a true physiological state. With a saturating inhibiting flash (ϕ) N is still inversely proportional to the background. Barlow, Fitzhugh & Kuffler (1957) and Westheimer (1970) have also concluded that lateral inhibition is independent of any particular class of receptor.

Thus differences in slopes of the incremental curves may be interpreted as a result of less extensive temporal summation of the a-wave and of the oscillatory potentials as compared to the b-wave at least within the range studied. Secondly there is probably a difference in spatial organization of the separate types of neurons generating the a-wave, b-wave and oscillatory potentials especially accentuated on exposure to background illumination of 1-10 cd/m².

It seems not unreasonable to assume that the oscillatory potentials reflecting the activity of cells of inner nuclear layer or internal plexiform layer or the amacrine cells express a function of an amplifier for visual information improving time and space resolution of visual signals received from the receptors as suggested by Maffei (1969).

There is no sign of rapid decrease in sensitivity of the electrical response to saturation on exposure to background light of $\log I_B = -1.0$ (around 1.2×10^4 scotopic td in the present study) or more. At this level of adaptation the human rods saturate (Aguilar & Stiles 1954; Rushton 1961). A saturation of the electric response was not expected in the present study since the ERG studied is mainly of the photopic type. As demonstrated psychophysically by Alpern, Rushton & Torri (1970b) threshold as a function of intensity does not saturate for cone vision. Only in the dimmest background illumination ($\log I_B = -5.0$) using stimulus light of low intensity ($\log I = -6.0$ and -5.0) a pure scotopic b wave was recorded in the present study.

The incremental threshold curves of the a wave and the oscillatory potentials are similar. This similarity in sensitivity of the a wave and the oscillatory potentials indicates that the a wave (reflecting activity of the receptor cells) must stimulate the regeneration of the oscillatory potentials.

The sensitivity of the b wave differed from that of the a wave and the oscillatory potentials which again suggests that the oscillatory potentials behave independently of the b wave and that the site of origin must be different.

On exposure to weak background light ($\log I_B = -5.0$) the oscillatory potentials seem to increase in a linear form in relation to stimulus light. In more moderate and intense background light ($\log I_B = -3.0$ to 0) the oscillatory potentials remain at about the same value when stimulus intensity increases. This is more distinctly demonstrated when the energy of the oscillatory potentials is calculated. Thus the change of the stimulus response curve seems to occur at the level of light adaptation at which the Purkinje shift of the b wave occurs (van Lith 1966) corresponding to about 1 cd/m ($\log I_B = -3.0$). This suggests that a dominating scotopic spectral sensitivity of the b wave seems to be a prerequisite for grading of the oscillatory potentials. Thus a prominent or isolated photopic activity as such does not seem to be able to modulate the oscillatory response at least with the stimulus intensity and stimulus interval used in this study. This stimulus response plateau also remains when the adaptation light is at and above the level of rod saturation ($\log I_B = -1.0$ and 0) (Aguilar & Stiles 1954; Rushton 1961).

In the brightest adapting light which bleached about 60% of the cone pigments (chlorolabe erythrolabe) and about 30% of rhodospin (Rushton 1958,

59 1963 1965 1966) there is a remarkable change in frequency of the oscillatory potentials when stimulus intensity is varied (Fig. 6). The oscillatory potentials recorded just at threshold have a high frequency (around 160 Hz) but in response to more intense stimulus intensities the frequency falls to a much lower level (around 120 Hz). This is in agreement with the frequency changes of the oscillatory potentials recorded in dark adaptation (Algerey-Wachtmeister & Westbeck 1972). Thus the bleaching of photopigments has not induced a decline in frequency of the oscillatory potentials. The alteration in frequency must be based on other events of the retina, probably changes in neural organization, i.e. in the inner nuclear or internal plexiform layer of the retina (Kuffler 1953; Barlow, Itzhugh & Kuffler 1957; Gouras & Link 1966; Gouras 1966; Henn & Grusser 1969; Werblin 1970, 1971) as was suggested in a previous study (Algerey & Wachtmeister 1972).

The stimulus response curve for the a wave is nearly linear for quite a considerable range (Armington, Johnson & Riggs 1952; Bornschein & Goodman 1957; Algerey 1967). In the present study subsequent increments of the logarithm of intensity produce within a range of a few log units a linear increase of the amplitude of the a wave even though the stimulus flashes were delivered at an interval of 30 seconds. This indicates that not even the high intensity flashes used have any appreciable influence on this relationship nor does light adaptation by steady backgrounds seem to alter this stimulus response relation. This has also been demonstrated on rat's ERG (Dodt & Echte 1961) as well as in experiments on the LRP (late receptor potential) of monkey's ERG (Boynton & Whitten 1970). The process of recovery of the a wave is also completed earlier than that of the total ERG response (Elenius 1969).

The b wave displayed another function of stimulus response entirely different from that of the a wave and that of the oscillatory potentials. This indicates that the oscillatory potentials adapt independently from the a wave as well as the b wave. This also supports the view that the origin of the oscillatory potentials is independent of that of the a- and b wave (Bornschein & Goodman 1957; Jacobson, Hirose & Popkin 1967).

Thus there is nothing to suggest a photochemical explanation for a change in (i) sensitivity, (ii) range of graded response or (iii) adapting behaviour of the oscillatory potentials.

Acknowledgment

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RECORDINGS OF APPLANATING FORCE AT CONSTANT INTRAOCULAR PRESSURE

III Intraocular volume-pressure relationship studied in intact human eyes

BY

WILLIAM THORBURN

Displaced volumes plotted against three intraocular pressure levels are used for the calculation of a regression line the slope of which represents a linear volume pressure relationship. This slope was greater in eyes of young than in eyes of elderly subjects but was not influenced by the initial intraocular pressure. The volume displaced by applanation corresponding to a pressure change as calculated in this study was larger than expected if an average coefficient of ocular rigidity of 0.0215 was used.

Key words: applanation - constant intraocular pressure - force recording - intraocular pressure - ocular rigidity - volume pressure relationship

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Abbreviations

- P_a , applanation tonometry final reading
 P_t , intraocular pressure during the experiment
 V_1 , V_2 and V_3 , displaced volumes
 b , regression coefficient
 x_i , intersection of the regression line with the abscissa

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The average value of the coefficient of ocular rigidity 0.0215 as estimated by Friedenwald(6) is open to question. Grant's method of tonography is based on this figure but open manometric investigations of living human eyes(4) have deviated from this figure. This paper presents a method for determining the volume pressure relationship in the intact living human eye.

Materials and Methods

Three different groups of subjects were studied in the present investigation.

A Subjects aged between 23 and 29 years. These represented young healthy eyes. The refractive error was determined and they were examined with slitlamp and ophthalmoscopy. Eighteen subjects were studied in the experiments with recording of applanating force with three pressure steps. Repeated experiments were performed on selected subjects with smooth tracings i.e. oscillatory changes in the intraocular volume of low frequency were not pronounced(15).

B Healthy subjects aged between 57 and 73 years (average age 65) chosen at random. A total number of 51 subjects. In this group some border line pressures were found but none was eliminated. This group represented elderly healthy eyes.

C Subjects from a group of people with known ocular hypertension collected in 1961 and previously reported by Linnér & Stromberg(11). From their material one random group of 17 subjects was studied, now aged between 51 and 83 years (average age 64). The range of the intraocular pressure in this follow up group showed that there were some individuals with normal intraocular pressures but none was eliminated because of this. Distribution of the intraocular pressures in the groups B and C is shown in Fig. 1. It was not possible to carry out all parts of each experiment on each one of the old subjects.

In special purpose some additional subjects were studied. These subjects not included in the group reported above were chosen in order to get results where the influence of slow oscillatory changes of the intraocular volume was eliminated as far as possible (1). One eye of each of five subjects aged between 47 and 73 with known month recordings of applanating force was studied.

Apart from the ocular hypertension there were no signs of orbital or ocular disease in any of the eyes examined, neither had any surgery nor medical treatment been applied to any of them.

The experiments have been carried out with an apparatus which measures continuously the applanating force and which at the same time keeps the intraocular pressure at a nearly constant and known level. The apparatus and the procedures used on living human eyes are described elsewhere(14, 15). The applanated area is calculated according to the Lambert Fick law from the applanating force and intraocular pressure. The displaced volume can be estimated in different ways. In the present study it was assumed that it was a spherical segment with a radius of 4 mm and the bases are equal to the applanated area. Briefly the experimental procedures were as follows. With the subject in a sitting position the intraocular pressure was measured

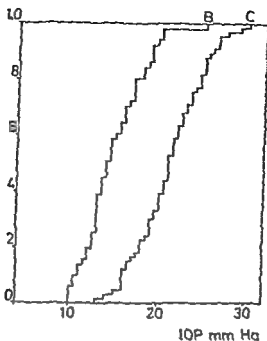


Fig 1

Intraocular pressure distribution in the groups B and C (see text). The mean of the intraocular pressure in the right and the left eye after repeated applanation measurements (abscissa) plotted against cumulative frequency (ordinata)

repeatedly by applanation tonometry and the stabilized reading (P_a) was accepted as the intraocular pressure on which the choice of P_i was based. The above apparatus was then applied and recording of the applanating force was performed with $P_i = P_a + 6$ mmHg for three minutes. Without interruption a rise in P_i to $P_a + 10$ mmHg followed for another three minutes and finally a short recording with $P_i = P_a + 15$ mmHg, followed (ascending pressure steps). Recording of the applanating force was also performed using the same P_i values in opposite order i.e. starting with a short recording at $P_a + 15$ mmHg followed by a three minutes recording at $P_a + 10$ mmHg and so on (descending pressure steps).

The method of applying stepwise changes in intraocular pressure made it possible to calculate the relationship between displaced volume and intraocular pressure on eyes in vivo. Firstly, the type of relationship was investigated by use of several steps. Secondly, recordings of applanating force with three pressure steps were studied with regard to the quantitative dependency.

To study the type of the relationship recordings of applanating force were performed on selected subjects during short periods of time at each P_i level. The displaced volume at each pressure step was calculated and the one corresponding to the pressure increase of 6 mmHg added to P_a was named l_1 . The next 4 mmHg pressure increase resulted in an additional displaced volume named l_2 and so on l_1, l_2, l_3 etc. were then plotted against the intraocular pressure as illustrated in Fig. 2. The

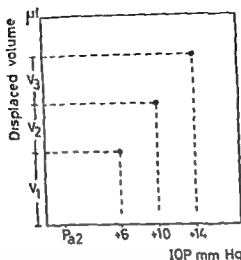


Fig 3

Schematic representation of the volume pressure relationship. Abscissa: intraocular pressure; ordinate: displaced volume. V_1 is the initial displaced volume and V_2 and V_3 are the increases in displaced volume at corresponding increases in intraocular pressure. P_{a2} represents the stabilized reading by applanation tonometry before the recording.

A line connecting the points represents the relationship between the displaced volume and the intraocular pressure.

The above method was applied to recordings of applanating force with three pressure steps. A regression line and its coefficient (b) on the three points experimentally determined according to Fig. 3 were calculated. The symbol x stands for the intersection of the regression line with the abscissa and was compared with the value of P .

Statistical method. When repeated experiments were performed on subjects of group A the figures of the random recording of applanating force of each subject were used. Comparisons were made between young and elderly healthy eyes (groups A and B) and between elderly eyes with normal ocular tension and with ocular hypertension (groups B and C). The differences were analysed by use of the method of multiple comparisons in multivariate analysis of variance and are presented as simultaneous confidence intervals (level 0.9) for differences of means.

If the confidence interval includes zero, no statistically significant difference between the means is obtained using a two-sided test at the 5% significance level. Simultaneous confidence interval involves a constant probability for all true differences in a study, not only for each one singly (13).

Results

The volume pressure relationship studied in one eye of each of five selected subjects is presented in Fig 3. A line fitting the points is drawn. It appears from the figure that a straight line gives a good approximation of the relationship. This result has led to the conclusion that within the range investigated the volume pressure relationship is linear within the errors of the method. A linear relationship is therefore applied throughout the present study.

The results of repeated recordings of displating force with ascending pressure steps on the right eye of thirteen young subjects (group A) are presented

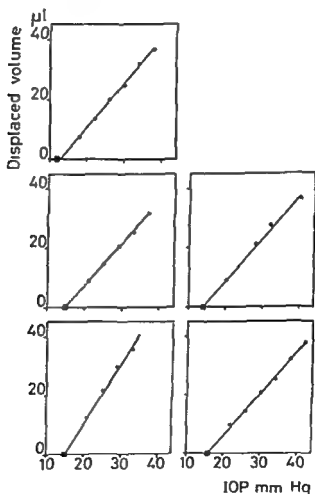


Fig 3

The volume pressure relationship in five eyes as illustrated in Fig . A line fitting the points is drawn. The square represents the P_a .

Force Recordings at Constant IOP III

in Table I together with the refractive error of each subject. There was a considerable variation in the b value within one and the same eye in different experiments and the difference between the different eyes was also large. Studying recordings of applanating force with descending pressure steps from the right eye of eight of the above subjects the results are similar (Table II). No significant difference between the b values of ascending and descending pressure steps was found.

No obvious connection between the degree of refractive error and the volume pressure relationship in these subjects was found.

Recordings of the applanating force with three ascending pressure steps from the three groups of subjects (A, B and C) were studied. No significant difference was found between the right and left eyes. In Table III are presented the mean and standard deviation of the displaced volumes at the pressure steps, the regression coefficient (b) and the value of the intersection with the abscissa (x) of the right eyes. Analysing differences between the groups, the b value differed between the group A on one side and the groups B and C on the other side (Table IV) while the intraocular pressure differed between the group C on one side and the groups A and B on the other side.

Table I

The refractive error of each eye and its volume pressure relationship expressed as the regression coefficient (b). Recordings of applanating force with ascending pressure steps from the right eye of young subjects (group A)

Subject	Refractive error D	No. of recordings	b mean	b range
1	-1.25 -1.90	5	9.1	1.9-9.4
2	-2.0	4	1.7	0.5-3.1
3	-3.0	3	1.7	1.5-9.1
5	+1.0	1	1.5	
6	-2.5 -4.0	3	1.3	1.2-1.5
7	+0.5	-	6	1.4-1
9	0	3	-1	0.6-9
10	-1.5	3	1.6	2.0-2.2
11	0	1	9.3	1.1-1.9
12	+0.5	9	1.6	
13	-0.5	1	1.9	1.6-1

Results

The volume pressure relationship studied in one eye of each of five selected subjects is presented in Fig 3. A line fitting the points is drawn. It appears from the figure that a straight line gives a good approximation of the relationship. This result has led to the conclusion that within the range investigated the volume pressure relationship is linear within the errors of the method. A linear relationship is therefore applied throughout the present study.

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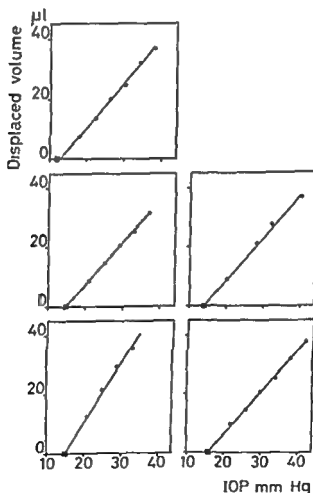


Fig 3

The volume pressure relationship in five eyes as illustrated in Fig 2. A line fitting the points is drawn. The square represents the P_a .

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Table I

The refractive error of each eye and its volume pressure relationship expressed as the regression coefficient (b). Recordings of applanating force with ascending pressure steps from the right eye of young subjects (group A).

Subject	Refractive error D	No of recordings	b mean	b range
1	- 1.75	3	21	18-24
2	- 1.90	2	27	22-31
3	- 2.0	2	17	15-18
4	- 3.0	3	17	15-21
5	+ 1.0	1	15	
6	- 2.5	3	13	10-15
7	- 4.0	2	16	14-17
8	+ 0.5	2	26	26-27
9	0	3	21	20-22
10	- 6.5	3	16	11-18
11	0	1	23	
12	+ 0.5	2	16	16-17
13	- 0.5	1	19	

Results

The volume pressure relationship studied in one eye of each of five selected subjects is presented in Fig. 3. A line fitting the points is drawn. It appears from the figure that a straight line gives a good approximation of the relationship. This result has led to the conclusion that within the range investigated the volume pressure relationship is linear within the errors of the method. A linear relationship is therefore applied throughout the present study.

The results of repeated recordings of applanating force with ascending pressure steps on the right eye of thirteen young subjects (group A) are presented

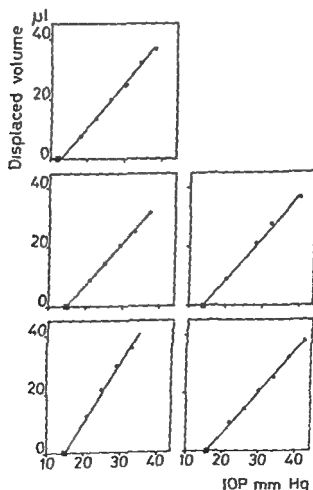


Fig. 3

The volume pressure relationship in five eyes as illustrated in Fig. 2. A line fitting the points is drawn. The square represents the P_a .

Table II

Simultaneous confidence intervals (level 0.95) for differences between means of the groups (Table III) obtained by the method of multiple comparisons in a multivariate analysis of variance

Variable		A-B	A-C	B-C
P	\bar{D} C I		-69 -97 to -41	-54 -75 to -32
b	\bar{D} C I	0.57 0.17 to 0.87	0.60 0.06 to 0.94	

\bar{D} mean difference C I confidence interval

Discussion

By use of the present method the relationship between intraocular pressure and displaced volume was approximately linear within the pressure range investigated (Fig 3). Previously the relationship was estimated by Friedenwald(6) being semilogarithmic. These observations were however based on measurements on enucleated human eyes. The effects of the effective perfusion pressure in the intraocular vascular bed on ocular rigidity are discussed by Blumenthal et al (2). Their results indicated that ocular blood volume exerts a major influence on ocular rigidity when measured by their manometric techniques.

The relationship between intraocular pressure and displaced volume studied by the present method may be influenced by rapid changes in the fluid content of the eye and changes in scleral distention. A slow change in scleral distention (12) during three minutes at each pressure level does not seem to be a factor of importance as very nearly the same volume pressure relationship appeared at ascending and descending pressure steps (Table I and II). The results indicate that in a selected group of young subjects there is no constant relationship between displaced volume and intraocular pressure but variations exist between different eyes and to some extent within one and the same eye (Table I). Concerning the variance between young subjects it is of interest to compare the results of Ytteborg(16) on the amount of expelled blood which varied greatly between different eyes at similar pressure levels.

The difference between the P_a and the x (Table III) represents the sum

Table II

The refractive error of each eye and its volume pressure relationship expressed as the regression coefficient (b) Recordings of applanating force with descending pressure steps from the right eye of young subjects selected from the group in Table I

Subject	Refractive error D	No of recordings	b mean	b range
1	-1.25	2	2.1	2.0-2.1
4	-3.0	2	1.7	1.5-1.9
6	-2.5	2	1.5	1.4-1.6
7	-4.0	1	2.6	
8	+0.5	2	2.8	2.7-2.9
9	0	2	1.9	1.7-1.8
10	-6.5	2	1.9	1.8-2.0
12	+0.5	2	1.4	1.0-1.5

Table III

Calculated displaced volumes (nl) at stepwise increase in intraocular pressure l , displaced volume corresponding to the first pressure increase of 6 mmHg l' and l_2 the same at the following steps of 4 and 5 mmHg respectively b stands for the regression coefficient ($nl/mmHg$) and P_0 the value of the intersection with the abscissa

Group		l	l'	l_2	b	P_0	l_1	$P_0 - l_1$
A $n = 18$	mean	9.4	17.2	26.0	1.84	19.6	14.0	-0.4
	SD	3.1	4.5	5.6	0.54	3.0	3.0	3.0
B $n = 41$	mean	7.4	12.7	19.3	1.33	15.2	15.7	-0.3
	SD	2.4	3.4	4.6	0.34	3.0	3.3	1.7
C $n = 46$	mean	7.3	12.6	18.5	1.25	20.5	20.3	0.3
	SD	2.5	3.0	4.3	0.35	3.4	3.9	2.3

n number of subjects SD standard deviation

sure level of 10 mmHg and smaller at larger applanated areas. The variance between eyes accounted as a rule for 80 % of the total variance. The error due to these uncertainties will of course mainly affect the V_1 value and to a much less extent affect the V_2 value. It is reasonable to believe that variations of blood content in the eye during the recording of applanating force can contribute to the variance of $P_o - x_o$.

The volume pressure relationship has by the present method as an average turned out to be different between eyes of young and elderly subjects (Table III). An increasing rigidity of the ocular coats was considered characteristic of advancing age by Friedenwald in 1937(6). On the other hand there was no significant difference in volume pressure relationship between groups B and C in spite of the fact that they represent two different intraocular pressure levels. The difference between young and elderly subjects is compatible with the assumption of an increasing rigidity of the sclera with increasing age. Another possibility is that a smaller amount of blood is expelled by the increase in intraocular pressure in elderly subjects and that this blood volume is the same at the different intraocular pressure levels in the two elderly groups.

The presented results differ clearly from the volume pressure relationship based on a coefficient of ocular rigidity of 0.0215. Fig. 4 shows the mean displaced volumes which are calculated from recordings of applanating force with three ascending pressure steps on the right eyes of groups A and B (from

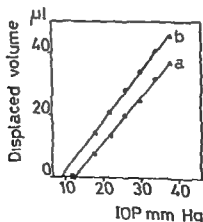


Fig. 5

The volume pressure relationship in one eye. Displaced volumes calculated as spherical segments (a) and by use of the experimental results of Linner(10) (b). The square represents the P

of errors of the measurement of P_{a2} and of P_t as well as the errors of the assumption concerning calculation of displaced volume and a linear volume pressure relationship. The variance of this difference (Table III) may be due to an uncertainty in the measurement of P_{a2} and of P_t . The P_{a2} is measured with a Draeger applanation tonometer and the accuracy of the readings is similar to those made with a Goldmann tonometer(35). The accuracy of the P_t -determination based on measurements on enucleated human eyes is discussed in a previous paper(14). At an applanated area of about 20 mm the standard error of the mean of the intraocular pressure was 0.4 mmHg at an intraocular pressure level of 40 mmHg and 0.2 mmHg at an intraocular pres-

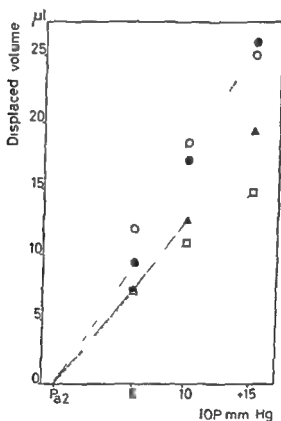


Fig. 4

The volume pressure relationship in the eye ● represents the mean values of the displaced volumes (from Table III) plotted against intraocular pressure in young subjects (group A mean $P_{a2} = 13.6$ mmHg) ▲ represents the same in elderly subjects (group B mean $P_{a2} = 15.2$ mmHg) □ represents the volume pressure relationship obtained by use of a coefficient of ocular rigidity of 0.0215 and an intraocular pressure of 14 mmHg ○ represents the corresponding volumes based on the figures of Langham(5) and an intraocular pressure of 14 mmHg

Calculations of the displaced volume according to the results of Linner give larger values (cf Fig 5). Comparing the values of the displaced volumes based on this calculation with the figures of Langham(8) all the values of elderly subjects (group B) clearly exceeds those of Langham. No certain conclusions can be drawn from these comparisons.

Using an average coefficient of ocular rigidity of 0.0215 the calculated change in volume due to a change in intraocular pressure thus results in an underestimation. The reason for this underestimation is probably the effect of the vascular bed, i.e. the volume pressure relationship is due partly to the physical properties of the sclera and partly to the change in the content of blood at the change in intraocular pressure. The importance of the ocular rigidity in calculation of facility of aqueous outflow based on measurement with a Schiotz tonometer was discussed by Becker & Friedenwald(1). If the conclusion above is applied to this procedure the volume change due to the change in intraocular pressure is underestimated. This was previously stressed by Eisenlohr et al (4). The variations between different eyes as well as within one and the same eye as observed in the present study (Table I and II) further increase the uncertainties in volume estimation.

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Table III) The mean P_a of the corresponding experiments was 13.6 mmHg in the group A and 15.2 mmHg in the group B. The volume required to increase the intraocular pressure from 14 mmHg to the corresponding pressures using a coefficient of ocular rigidity of 0.0215 is shown in the same figure. An overestimation of the applanated area in the present method(14) can only explain a part of the difference.

The volume displaced by applanation can be calculated in different ways. As mentioned above in the present method the calculation is based on the treatment of the displaced volume as a spherical segment which is taken as the lower limit value(14). Using the results of Linnér(10) based on experiments performed on intact enucleated human eyes and thereby including possible additional deformation besides the applanation of the cornea the values of displaced volume become larger. An example of both ways of calculating the displaced volume is shown in Fig. 3. Recalculation of the present results by use of the figures of Linnér(10) makes the difference from the volume pressure relationship based on a coefficient of 0.0215 still more pronounced.

Langham & Eisenlohr(9) in open manometric studies of the pressure volume relationship in living human eyes found good agreement between the results of different investigations. Langham's figures(9) are based on measurements on six eyes the patients were aged between 39 and 66 years mean age 54. His volume figures corresponding to the pressure steps in the present study using an initial intraocular pressure of 14 mmHg are also shown in Fig. 4. Comparing the results of the present study based on calculations of the displaced volume as a spherical segment Langham's volume measurements give larger values with a smaller increase of the intraocular pressure. At the greatest pressure increase there is a better agreement between his values and those for young subjects (group A) of the present study but his values still exceed those of the elderly subjects (group B). Using values of 1, 1 and 1.3 based on the figures of Langham(9) for calculation of the regression coefficient the found value falls between those of the groups A and B i.e. those of young and elderly subjects.

There is however a fundamental difference between the results of Langham and the results obtained by calculating the displaced volume as a spherical segment, as such a calculation does not include a possible additional deformation of the eye ball besides the applanation of the cornea. The difference shown in Fig. 4 might very well be explained by the fact that Langham's figures are obtained without deformation of the eye ball while the applanation of the cornea of the living eye might induce an additional deformation. The results of Linnér(10) are as mentioned above including a possible deformation of the eye ball but are however obtained in enucleated eyes.

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Alex E Krill Hereditary Retinal and Choroidal Diseases Volume I Evaluation Harper & Row 1972 DM 75⁰⁰

This is a very important book on the principles and actual performance of diagnostic technology pertinent to diseases of the fundus of the eye. Many of the diseases discussed are genetic and so the first chapter contains genetic principles including inborn errors of metabolism and pharmacogenetics. There is an introduction to cytogenetics that will enable ophthalmologists without previous background on the topic to understand the pathogenetics of chromosomal aberrations and the Chicago nomenclature of 1966 which is presented in a lucid didactic style.

One third of the book, namely the chapter on fluorescein angiography, is written by Desmond Archer. This is a comprehensive introduction including the theory of hydrodynamics of the dye and a discussion of the ultrastructure of the posterior layers of the eye concentrating on the junctional complexes of the vessel walls and the pigment epithelium which is of importance for the penetration of the dye.

The angiograms of pathological conditions are of high quality and very informative. It is curious that Archer's name does not appear on the title page or in the list of contents.

It is in the area of dark adaptation and electroretinography that Krill did most of his original work and the chapters on these procedures are of particular interest to both physiologists and clinicians. The pathophysiology and the instrument are presented in a very clear and simple yet beautiful language. There are many examples of important pathological conditions but a full clinical description of the hereditary retinal and choroidal diseases was planned to appear in volume II.

In the discussion of electroretinography in which Krill was particularly experienced we find an important survey of the range of variation of the waves of scotopic and photopic ERG, their amplitude and implicit time during adaptation and with varying intensity of light.

Short chapters on electrooculography, visually evoked response and color vision evaluation finish the book. These chapters concentrate mainly on the practical application of the tests.

This is a book that demonstrates the high standard of work that was going on in Krill's laboratory when an aircraft accident cruelly terminated his brilliant career. His insight in basic physiology paired with clinical experience and imagination has added much new knowledge to our discipline. Volume II will contain most of the clinical work of Krill and his coworkers during the last ten years and hopefully this will soon be published. We shall miss him intensely but the loss of this kind and intelligent man is hardest to bear for Suzanne and Eileen to whom this book was dedicated.

Mette Warburg

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THE ISOTONOMETRIC COMPRESSION TEST

BY

O TIERI A POLZELLA and V IURA

A description is given of a test for determining the outflow of the aqueous humour. The test consists of compressing the eyeball with a metal funnel attached near the limbus of the cornea by suction. The intraocular pressure increased in this way is kept constant during the test by increasing the suction. The intraocular pressure value is continuously controlled by an applanation tonometer. The results are based on the amount of extra suction that is necessary to keep the intraocular pressure constant.

Key words: aqueous dynamics - tonography - glaucoma screening tests - outflow facility - ocular rigidity and outflow

The methods used for a more or less quantitative determination of the outflow of the aqueous are based on the fact that compression of the eyeball increases the normal fluid outflow thereby causing a decrease in the volume of the contents of the eyeball and accordingly of the intraocular pressure as well.

All the methods that are based on this principle have the same shortcoming namely that the volumetric variation is indirectly calculated from the pressure variations thus introducing a serious source of error the degree of which can

Preliminary papers on this subject have been presented to the Italian Society of Experimental Biology (Tieri 1970a, b; Tieri, Polzella & Iura 1971).
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*Vereinigung Bayerischer Augenärzte und
der Österreichischen Ophthalmologischen Gesellschaft*

Gemeinsame Tagung der Vereinigung Bayrischer Augenärzte und der Österreichischen Ophthalmologischen Gesellschaft vom 31. Mai bis zum 2. Juni 1973 in Würzburg

Als Hauptthema ist Glaukom geplant als Nebenthema Psyche und Auge. Daneben sind freie Vorträge zugelassen. Anfragen: Prof. Dr. W. Leydhecker, Universitätsaugenklinik, Josef-Schneider-Str. 11, D-8700, Telefon 2 01 24 02.

The 2nd World Congress on Ultrasonics in Medicine

Rotterdam, June 4-8, 1973. Themes: neurology, internal medicine, cardiology, gynecology, ophthalmology, and physics. Sekretariat: c/o Holland Organizing Centre, 16 Lange Voorhout, The Hague, The Netherlands.

International Eye Foundation Society of Eye Surgeons Congress

The Second Congress of the Society of Eye Surgeons of the International Eye Foundation will be held in Athens, Greece, from September 4 through 6, 1973, with the collaboration of the Greek Ophthalmological Society. The theme will be "Complications and the Handling of Unusual Surgical Cases," covering all aspects of major ophthalmic surgery. Special lectures will be given by Professor Louis Paufigue, Lyon, France (Vail Medal recipient) and by Professor Irving H. Leopold, USA (the first Atkinson Lecturer) on "Advances in Anesthesia for Ophthalmic Surgery."

The Congress is open to non-members on a limited basis.

For further information write: Box A, Society of Eye Surgeons, International Eye Foundation, 5225 Loughborough Road, N.W., Washington, D.C. 20016.

this intraocular pressure value is kept constant during the test by progressively increasing compression of the eye. During the compression the intraocular pressure is continuously controlled with a Goldmann applanation tonometer and the outflow of aqueous fluid is determined from the value of the external compression that is necessary to keep the intraocular pressure constant during the test.

Experimental Evaluation

On the basis of the above considerations we constructed an apparatus for compression of the eyeball similar to those described by Evans & Klein (1959) and by Galin et al (1969). This consists of a metal syringe with a perfect fit and a capacity of 100 ml the piston of which can be moved by turning a screw around its threaded rod. To this syringe a T tube is attached one channel is connected with a mercury manometer the other with a small metal funnel (internal diameter = 12 mm flange = 1 mm) (Fig 1).

The test is very easily performed. Into the conjunctival sac we repeatedly instil an anaesthetic solution (Novesine Wander 0.4%) After 2 min we instil one drop of a solution of the following composition (in g/100 ml)

carboxymethyl cellulose	0.250
naphthyl methyl imidazoline	0.025
sulphacetamide	1.500

This instillation has two purposes: it reduces the secretion of tears which during the test might lead to a dilution of the dye and thus prevent precise determination of the pressure; and secondly the presence of a small quantity of methyl cellulose effectively protects the corneal epithelium from damage. The collyrium that we use does not interfere with the determination of the ophthalmic tone. Preparation of the patient is completed by removing excess fluid in the conjunctival sac with a piece of sterile gauze after which the precorneal film is coloured with fluorescein using standard strips of paper soaked in the dye.

The intraocular pressure is determined with the Goldmann applanation tonometer. We then begin to compress the eyeball placing the metal funnel on the sclera (in the temporal sector on the horizontal meridian at a minimal distance of 7 mm from the corneal limbus) and moving the plunger of the syringe to an aspiration of 50 or 100 mmHg. The funnel should not be applied too far posteriorly i.e. towards the external palpebral commissure because here the compression causes a circular subconjunctival ecchymosis. This renders

not be precisely determined. The ocular rigidity which is the specific ratio between the pressure and the volume of the given eye examined varies from one individual to another and may also vary in the same individual (Gloster 1966). Attempts to correct the error caused by the ocular rigidity by calculating aqueous outflow in various ways (Friedenwald 1954 or Goldmann & Schmidt 1957) have hitherto had an adverse effect because of the intrinsic lack of accuracy of these methods (Etienne 1969). Furthermore the change in the ocular pressure caused by compression also leads to a shift of choroidal blood during the estimation in that the blood is first forced out of the eye and then when the ophthalmic tonus decreases it again flows back into the eye. Thus the pressure variation recorded is also a manifestation of this factor and therefore masks the factor that we wish to determine namely the volume of aqueous fluid that flows out (Gloster 1966).

These restrictions have been pointed out by research workers who have interested themselves in tonography, a method which is meant to be a physiological exploration of the hydrodynamics of the eye. Various methods of isotonography have been proposed with the idea of keeping the intraocular pressure constant during the test (Moses 1957 van Beuningen 1958 Goldmann 1958 Priot 1959). The most serious shortcoming of these methods apart from their complicated nature is the lack of accuracy of the available tonometric calibrations (Ourgaard & Etienne 1961) and in particular the fact that there are no calibrations for tonometer weights intermediate between those commonly used (Gloster 1966).

Stepanik (1968) proposed a method of "applanation rheometry" with progressive compression of the eyeball effected in such a way as to keep the ophthalmic tone constant. The indentation volumes are calculated by photographing the area of applanation and determining the radius of the internal curvature of the cornea. However ingenious this method is it is not very practical and unfortunately has also many sources of error.

Moses (1966 1967a b) has proposed a method of applanation isotonography utilizing the Mackay-Marg tonometer. The principal shortcoming of Moses' method is that the indentation values used are so small (approx. 8μ) that this method cannot be used for those cases with a pronounced ocular rigidity or with higher than average outflow values.

Linnér & Thornburn (1961) described the principles of a technique for applanation isotonography. An apparatus is used to increase the intraocular pressure and can keep it constant at a known level so that the applanation area can be measured and the volume of fluid displaced can be calculated.

By our method for studying the outflow of aqueous fluid a standardized pressure is exerted on the sclera causing an increase of the ophthalmic tone

this intraocular pressure value is kept constant during the test by progressively increasing compression of the eye. During the compression the intraocular pressure is continuously controlled with a Goldmann applanation tonometer and the outflow of aqueous fluid is determined from the value of the external compression that is necessary to keep the intraocular pressure constant during the test.

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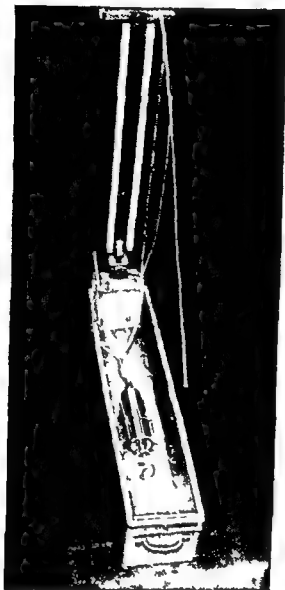


Fig 1
The bulbar compressor

the test invalid because part of the suction force applied is used not only to compress the eyeball but it also aspirates blood from the tissue under the cup. This causes the outflow to seem better than it actually is (see Fig 2).

Once the desired suction value is reached the corresponding ocular pressure is read (P_1). The graduated drum of the tonometer is then not touched any more. Perfect collimation of the two semicircumferences is maintained by increasing the suction for 4 min (See Fig 3). (We have used this period of 4



Fig 2

Correct position of funnel on the sclera. At the same time the prism of the applanation tonometer is in contact with the cornea

minutes because it is the period used for tonography it can probably be reduced in view of the absence of disturbing factors during the early phases of the test) After this time the suction value is carried back to the initial value and the corresponding intraocular pressure (P_1) is read. Finally suction is discontinued the funnel is removed from the sclera and the intraocular pressure is measured once more (P_2).

The initial suction value and the progressive suction values up to the 4th minute are recorded every 30 seconds. The difference between the 4 min suction and the initial suction is used to evaluate the outflow of aqueous fluid.

The intraocular pressure values (P_1 , P_2) obtained with this test can further be used for an eyeball compression test similar to Blaxter's test (modified by Evans & Klein 1959) with this significant difference that under the conditions described by us an isotonometric compression is applied. The pressure values obtained prior to compression (P_1) and at the end of the compression (P_2) may also be used for evaluation of the outflow according to the concept of K. Suda (Ourgaud & Etienne 1961). Elsewhere we shall publish a report of the results of a comparison of the findings obtained by these different methods of interpretation.

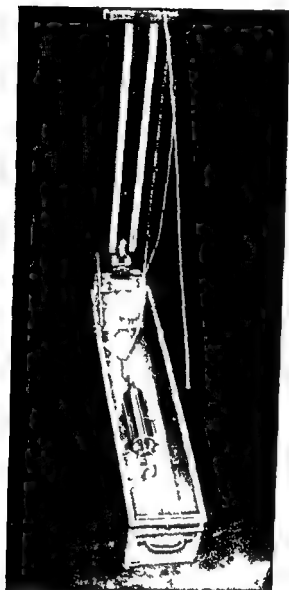


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The Isotonometric Compression Test

Table I

Aqueous outflow values ($\mu\text{l}/\text{min}/\text{mmHg}$) in normal subjects with isotonometric compression test. The results with two different suction values are reported.

	Suction value	
	-50 mmHg	-100 mmHg
n	43	27
M	0.47	0.23
DS	± 0.02	± 0.03

Table I shows that values found for the outflow of aqueous fluid using two different suction levels (50 or 100 mmHg) differ considerably. With less suction the outflow value appears to be higher.

We prefer a suction value of 50 mmHg, also because in practice lower values make it difficult to keep the aspiration funnel stable. With lower suction values the funnel easily detaches itself from the eyeball. Furthermore, lower suction values have the disadvantage that they do not always cause a sufficient increase of the intraocular pressure.

The values listed in Table I have been calculated as follows:

$$\text{outflow facility } C = \Delta V / \Delta P \cdot t$$

in which

ΔV = volume of fluid driven out of the eye during the test. It is evaluated from the suction difference between the beginning and the end of the test (i.e. the suction value necessary to keep the intraocular pressure constant).

ΔP = the difference between the intraocular pressure during the compression and the initial intraocular pressure ($P_1 - P_0$). (No correction has been made for any increase in episcleral pressure.)

t = time (in this case 4 minutes).

Discussion

The isotonometric compression test that we propose is very simple to perform and does not require any special skill. Reasonable familiarity with the technique of applanation tonometry suffices.

Our test can also be applied to subjects with only one eye, because the fixation of the eye that is examined is not impaired by the presence of an opaque tonometer. As a rule, the subject adequately fixes the illuminated cone of the Goldmann tonometer.



Fig. 3

The performance of the isotonometric compression test

Results

We report below the results obtained for normal subjects using the isotonometric compression method. These tests were done with a suction of 100 mmHg in a first group and 50 mm in a second group of subjects.

During our determination with an initial suction of 100 mmHg we encountered difficulties in accurately reading small differences of intraocular pressure with the applanation tonometer when the pressure values were approx. 50 mmHg. Since correct performance of the technique we propose is based precisely on the continuous correction of the pressure differences that tend to occur in the course of the test, it became evident that it was advisable to work with pressure values low enough to ensure accurate tonometer readings. A suction of 50 mmHg gives intraocular pressures of approx. 90 mmHg which are suitable for our purposes.

The Isotonometric Compression Test

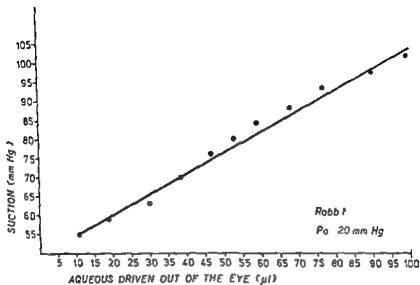


Fig 5

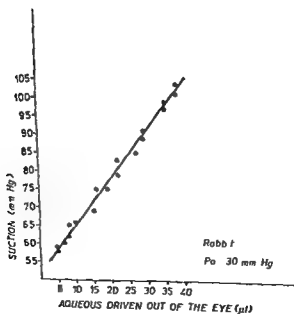


Fig 6

The patient's position is also comfortable as it allows him to sit in front of the slit lamp with normal posture he is not in any unusual situation that would cause apprehension and result in a state of tension and there are no problems of venous stasis due to posture of head in relation to the trunk of the body

The advantages to the observer are also obvious. It is no longer necessary to keep the tonometer immobile for the 4 minutes required by tonography he has only to regulate with one hand the progressive increase of the suction and to control with the other the position of the tonometer on the cornea and to modify this if necessary. The cost of the apparatus is very low as it is only necessary to construct the suction system and the mercury manometer as now days every specialist already possesses an applanation tonometer.

The theoretical advantages of the isotonometric compression test over the other methods of evaluation of the outflow of the aqueous fluid are implicit in the basic considerations involved the elimination of the ocular rigidity as a source of error is undoubtedly an enormous advantage especially in those cases (myopia sequelae of operations on the eyeball) in which the rigidity greatly differs from the average rigidity.

A very important problem is that of the ratio of the suction brought about and the corresponding scleral indentation and this must be solved if the isotonometric compression test is ever to be usable as a means of quantitatively analysing the dynamics of the aqueous fluid.

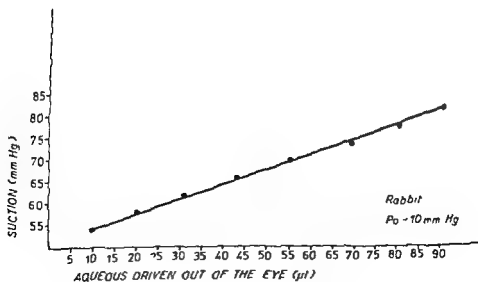


Fig 4

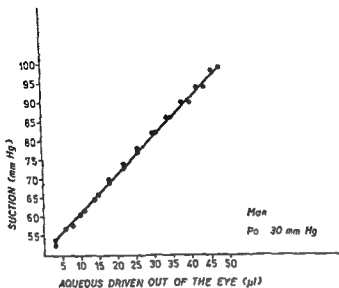


Fig 9

Doubtless as also asserted by Podos Minas & Macri (1968) in connection with the measurement of the episcleral venous pressure part of the force exerted serves to compress the conjunctival tissue and the scleral wall. However this fraction is constant as is proved by the precise correlation between the episcleral venous pressure measured by vascular compression and those obtained by direct cannulation. Also as is stated by Galin et al (1969) with identical suction cups and the same initial pressure and ocular rigidity a given suction value will cause the same pressure increase in different eyes. This means that the partial dispersion of the force is constant and may accordingly be neglected in the evaluation of the indentation volumes.

In any case the influence of this factor is limited to the preliminary phases of the test once the funnel has been applied all interference of this nature becomes negligible.

Our experiments with direct measurements of the scleral indentation volumes corresponding to the different suction values confirm that there is a good correlation between these two parameters (Tierl & Iolozella 1972). Technical details of the calibrations are given elsewhere here we report the results obtained on living and enucleated rabbit eyes and one human eye enucleated immediately before our experiments owing to the presence of a small choroidal

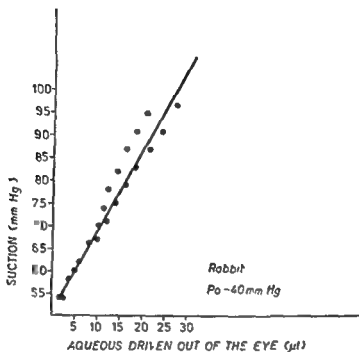


Fig 7

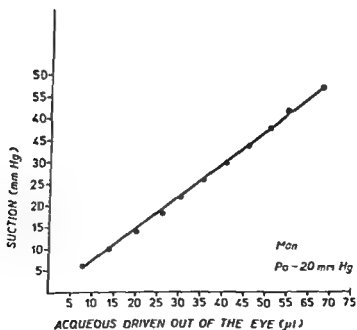


Fig 8

The Isotonometric Compression Test

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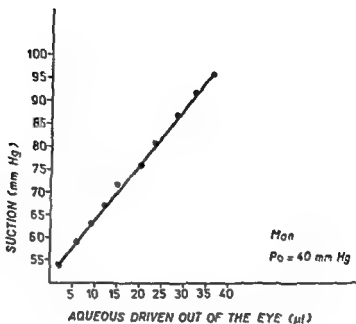


Fig 10

sarcoma in the posterior pole. The scleral wall was normal, the intraocular pressure 10 mmHg, and the corneal radius of curvature 7.9 mm.

Figs 4-7 concern the rabbit eye and four values of intraocular pressure are considered: 10, 20, 30, and 40 mmHg. In Figs 8-10 are reported the results for the human eye for three pressure values (20, 30, and 40 mmHg). Both in the rabbit and in man there exists a good correlation between a given suction value and the corresponding volume of scleral indentation. In the rabbit much more so than in the man, the volume of indentation corresponding to a given suction value is progressively lessened with an increase in the intraocular pressure.

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LAMELLAR KERATECTOMY BY THE METHOD OF GUNDERSEN

BY

J. HVIDBERG HANSEN and P. M. MØLLER

Keratectomy followed by conjunctival keratoplasty is described in several modifications of the method used originally by Gundersen. Of 60 patients 44 were seen at follow up. The great majority were satisfied with the operation which is distinguished in particular by promptly relieving pain.

Key words: corneal diseases - conjunctival keratoplasty - follow up

Corneal diseases may be treated by several surgical procedures including lamellar and penetrating keratoplasty.

In 1958 Trygve Gundersen described a simple procedure consisting of keratectomy and covering by the bulbar conjunctiva. The suggested indications were various corneal diseases e.g. severe herpetic infections, bullous keratopathy, filamentous keratitis, traumatic recurrent keratitis and neuroparalytic keratitis. In a subsequent publication Gundersen (1960) reported his experience in particular in the treatment of bullous keratopathy. In this paper he described an improved technique including complete conjunctival covering following keratectomy of the peripheral parts of the cornea leaving a central circular islet from which the conjunctival mucosa could later be removed. From our department Wille Jørgensen (1966) published the results of treating bullous kera-

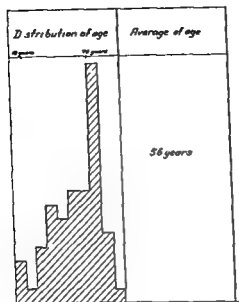


Fig. 1

Histogram of the age distribution in the material

titis by the method of Gundersen. The experience gained at that time encouraged further application of the procedure, and in the course of time it has been used successfully also for other corneal diseases, including those originally suggested by Gundersen.

Below the operative methods the primary results and the subsequent course assessed by follow-up examinations will be reported.

Material

The material comprises 60 patients, all treated in the Eye Department of the Odense Hospital during the period 1962-1970. During this period a total of about 6200 patients were admitted. The age distribution is shown in Fig. 1. Thirty-six were males and 24 were females.

The corneal diseases that were treated are listed in Table I. There were two groups of almost equal size, viz. the corneal diseases which were complicated by bullous keratopathy and those in which this manifestation was not present.

Table I
Distribution of corneal diseases in the material

Bullous keratopathy	Without former intraocular operations (Fuchs' dystrophy)	5	}	29
	With former intraocular operations (cataract extractions, glaucoma operations)	15		
	Various corruptions (lime)	4		
	Hemorrhagic glaucoma	4		
	Congenital glaucoma	1		
Keratitis	Herpetic ulcers	15	}	24
	Leukophthalmos	2		
	Keratoconus	1		
	Marginal ulcers	2		
	Various diseases (polyarthritis, sarcoidosis, herpes zoster)	4		
Complications after corneoscleral trephining (thin walled drainage bleb perforation following bleb inflammation)		4		4

Table II
Survey of follow up

Number of patients	Operated	Follow up	Dead	Enucleated eyes	Not examined
Total keratectomies	19	12	3	4	-
Partial keratectomies	32	24	4	1	3
Bridge keratectomies	9	8	1	-	-
Total	60	44	8	5	3

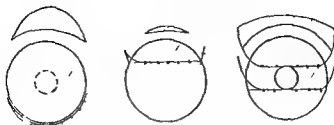


Fig. 2

Three main types of keratoplasty with conjunctival covering. On the left the technique originally described by Gundersen. Central non penetrating trephining preserving a central islet of intact cornea, except for the indicated epithelial denudation. In the middle a partial or semilunar keratoplasty and on the right the bridge shaped one in which a prepared flap of the bulbar conjunctiva over the cornea is pulled down. Centrally the keratectomy is omitted. The dotted areas represent areas denuded of conjunctiva. hatched areas keratectomized parts of the cornea.

Within these two groups the majority of the patients made up two sub groups: bullous keratopathy following ocular operation and sequelae to herpetic infection. Other causes contributed only a small number of patients. A special group was made up of complications consisting in a drainage bleb following fistulizing operation for glaucoma.

The follow up examinations were performed in the spring of 1971. At that time the follow up period was an average of 24 months, ranging from 6 months to 8 years. Table II gives the distribution and number of patients included in the follow up.

Method

For the conjunctival keratoplasty we used various modifications which may be grouped into three types (cf. Fig. 2). One method used partly the original Gundersen method and partly the subsequent modification leaving the central area intact. Because in both instances the conjunctival covering is complete no distinction will be made below between the two methods. On the other hand there is a fundamental difference between these methods and the subsequent ones viz. partial or semilunar keratoplasties in which only a peripheral part of the cornea is covered with conjunctiva following keratectomy and a type which we have called bridge keratoplasty in which a central or usually paracentral

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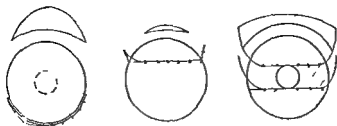


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Fig 3

Detail of the operation the keratectomized cornea merging directly with the conjunctiva



Fig 4

A patient with a severe limbal ulcer stained with fluorescein and rose bengal combined with two staphylococci



Fig 5

Same eye as in Fig 4 after partial keratectomy

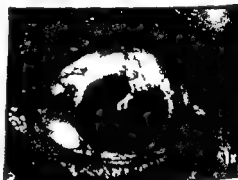


Fig 6

The result of suturing the conjunctiva to the keratectomized cornea after excision of a thin walled cystic drainage bleb

lesion is covered with a narrow band of conjunctiva in an attempt to preserve the visually important central part of the cornea

For covering the entire cornea we used the technique which Gunderson described in detail (1958 1960) and which has also been discussed and illustrated by Castroviejo (1966) Our customary procedure was described by Wille Jorgensen (1966) so no details will be mentioned here However it may

he pointed out that covering may also be obtained by using mucosa from the superior as well as the inferior fornix collecting the conjunctiva at the middle or slightly below the middle of the cornea

Conjunctival covering of a peripheral corneal lesion is well known but it was not until the introduction of lamellar keratectomy that a permanent cover of the cornea was secured and this is significant with respect to a possible tendency for the primary lesion to recur. Let it be pointed out that in this type of procedure it is always desirable to use as thin a conjunctival flap as possible. In preparing such a flap it has proved advantageous to start by keratectomy beginning just central to the diseased area and when the keratectomy has reached the limbus to continue towards the subconjunctival space just outside the limbus. Thereby it is possible to detach the conjunctiva while preserving the connection to the keratectomized piece of the cornea which thereafter may be used for fixing the very thin layer of conjunctiva (Fig. 3). It is important to avoid keratoplasty by parts of Tenon's capsule as this may entail a tendency to ptosis.

In forming the bridge shaped keratoplasties we use a technique somewhat similar to Gundersen's original one. The principle is illustrated in Fig. 2. It should be emphasized that if at all possible keratectomy of the central area should be avoided but in some instances this may be impossible for example if this very area is covered with keratitis. Usually however a central area may be preserved. For at least three months the cornea has to be covered by the conjunctival bridge. Thereafter it is often possible to remove the conjunctival cover just in the central area whereupon the smooth epithelialized corneal surface can be exposed by a minimal intervention.

For bleb reconstructions we have successfully used a technique of modified lamellar keratectomy. After excision of the cystic or ruptured bleb we have pulled a thin conjunctival flap down from the superior fornix and sutured it to a keratectomized area immediately central to the fistular opening (Fig. 6).

All the keratectomies were performed with a Beaver knife and the conjunctiva was sutured with Virgin silk sutures 8-0.

The follow up examinations were conducted in the Eye Department of the Odense Hospital. After questioning the patients about the further course of the disease any complaints and any psychological problems we asked them to state their overall opinion of the operative result. After this we assessed the visual acuity, the ocular position and the adnexa. In the course of the examination an objective evaluation of the cosmetic result was attempted. Corneal sensibility was tested by Coiffignon's aesthesiometer and compared with the sensibility of the contralateral eye. Lastly a slit lamp study was done and all operated eyes were photographed with a Medical Nikor camera.

Results

The operative procedure described above cannot be said to belong to the technically difficult ones although caution is advisable in keratectomy on the diseased area. Perusal of the case records revealed that already on the first postoperative days 97% of the patients stated that the discomfort in the eye had subsided. Because of this the patients can quickly return to a more normal life and the stay in hospital after the operation was usually less than two weeks. From 1 month to 1 year after the operation five patients had enucleation (Table II) as the underlying disease proved so severe that this was inevitable.

In two cases partial conjunctival keratoplasty by the method of Cunderlen was later followed by corneal grafting.

During the period from the operation to follow up about 80% of the patients – not counting those who died – had no complaints at all in the eye. One patient had undergone tarsorrhaphy by the method of Elschning and in one case a herpetic infection recurred but this patient was in the terminal stage of cancer. Otherwise it is striking that the herpetic infections showed no tendency to recur whereas previously recurrences had been constant.

From Table II it is apparent that three-quarters of the material could be invited to attend follow up. Out of the 44 patients 42 stated that on the whole they were satisfied with the operation. Only one felt bothered by the somewhat ungainly cosmetic result which otherwise could be characterized as excellent in 30 cases, acceptable in 12 and poor in only two cases. These latter patients had had their operations at a very early stage of the trial period. One exhibited ptosis and the other one had a divergence and a somewhat thick conjunctival covering. A total of seven patients had mild ptosis, 10 had convergence whereas 33 showed parallel ocular axes. As might be expected the visual result was most favourable after partial keratoplasties and among the bridge keratoplasties there were also several patients with good vision. It is still too early to say anything about the results that may be expected after cutting bridges and opening the central area of total keratoplasties.

Slit lamp inspection of the cornea showed that the vascularity of the conjunctiva had decreased considerably during the follow up period. This could be confirmed by comparison with photos in cases where colour photos were available from the period immediately after the operation. A few patients exhibited such marked atrophy and pallor of the conjunctiva that it created an illusion of corneal epithelium and its true nature could be disclosed only in the slit lamp.

As to the result of conjunctival covering following keratectomy central to

the affected filtering bleb there was a favourable effect both in cases with a thin walled cystic bleb progressing over the cornea and in perforation of the bleb wall with subsequent intraocular infection (Spatinfektion). In the latter case antibiotic therapy had been administered prior to the operation.

Lastly the results of testing corneal sensibility. The sensibility was measured in all quadrants and centrally and it was compared with the sensibility in the contralateral eye always using an aesthesiometer. The results proved somewhat varying but on the whole the conjunctiva showed less sensibility a factor which in a couple of instances was instrumental in reducing irritation due to trichiasis.

Discussion

Many corneal diseases are extremely troublesome as they cause constant irritation, photophobia and epiphora. Gundersen's operation aims primarily at relieving the discomfort of chronic irritative diseases in eyes which for a long time have been merely a burden to the patient. Indeed it is characteristic that in the follow up the patients repeatedly emphasized the relief they felt after the operation which as a rule had entailed improvement on the very next day and as a whole had had an extremely reliable pain relieving effect.

The striking gradual smoothing and paling of the conjunctival mucosa which had become adherent to the cornea following keratectomy were mentioned also by Arentsen (1965). The conjunctival epithelium may create a nearly perfect illusion of corneal epithelium even in the slit lamp and only the atrophic vessels disclose the true nature of the tissue.

To a marked extent the patient's satisfaction appears to be independent of and unaffected by the fact that the visual function of the eye has deteriorated or at least not improved. The great majority of the patients however had good vision in the other eye and therefore they did not feel essentially bothered by the unilateral visual impairment. In any case a weak sighted but quiet eye seems to be preferable to an eye with constant irritation. In this connection it is important to point out what comfort it is to the patient to have a reserve eye having the possibility for re-established vision.

Enucleation following an attempt to save the eye will occur of course in a material with ocular diseases having such a serious prognosis as the present ones but it is beyond doubt that in a large number of further cases the only alternative to Gundersen's operation was enucleation. Thus it must be presumed that this operation has contributed to preserving several eyes and thus has afforded the possibility for subsequent reconstructive surgery such as corneal grafting.

The new differentiated procedures introduced in our department during the latter half of the follow up period have altered the indications for keratoplasty with conjunctival covering in the direction of using it also for younger patients and for less deleterious ocular diseases. Keratoplasty has now been used in a few cases of children with chronic troublesome corneal diseases that could be predicted to be going to entail scar formation and vascular invasion. In these procedures too the aim should be the simplest operative method which can afford the most rapid re-establishment of the greatest possible function. In some cases this was partial or semilunar keratoplasty whereas in others it was a bridge keratoplasty to cover corneal diseases located more centrally.

In the predominant majority of cases the alternative to Gundersen's operation in its various modifications is tarsorrhaphy which indeed had been used for the treatment of several of our patients prior to the conjunctival covering. The advantage of Gundersen's operation is compared with tarsorrhaphy is primarily its permanent character which as is apparent from the present study to a very great extent prevents recurrences of the primary disease. In addition we feel that Gundersen's operation affords more rapid and more perfect relief from pain than does tarsorrhaphy. Furthermore tarsorrhaphy prevents inspection of the cornea making it difficult to observe a possible abscess formation whereas this does not give rise to problems beneath the conjunctival covering. Lastly it must be emphasized that tarsorrhaphy occasionally entails scar formation with trichiasis.

The favourable results of keratectomy with conjunctival covering of a cystic bleb progressing over the cornea is in keeping with the statement of Fitzgerald & McCarthy (1962) that the cicatricial tissue in connection with keratectomy prevents progression of the bleb over the cornea.

Lately we have been using Gundersen's operation more in the form of partial/semilunar keratectomy with conjunctival cover and this method we have used in an increasing number of chronic marginal ulcers (figs 4 and 5). We have also used it with great success in acute herpetic keratitis outside the optic zone. Thus by the partial Gundersen we have been able to bring relief to acutely and chronically inflamed corneae also in cases where an abscess threatening to perforate has been a serious complication. The alternative to these procedures might be imagined to be acute lamellar keratoplasty but where the optic zone has not been involved our experience so far has been that keratectomy with conjunctival covering is vastly preferable.

All considered we are of the opinion that Gundersen's operation with the submitted modifications is a valuable supplement in the treatment of corneal diseases.

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particular biomicroscopy and fluorescein angiography it has been possible to analyse in more detail the changes in the small retinal vessels

There are relatively few reports concerning the early stages of angiomatosis retinae. According to Bedell (1931) the intraocular lesions are usually localized around the periphery of the fundus and the earliest clinical findings are dilatation and tortuosity of parallel arteries and veins. According to his observations papilloedema may appear either simultaneously or before the peripheral changes. Rumbaur (1941) observed very early changes in angiomatosis. He debated whether the angiomatous lesions or the changes in the feeding vessels constituted the primary clinical picture and came to the conclusion that either one of them could

Joe V. Spencer (1964) in a histological study described a capillary angioma in the retina of a patient who died after extirpation of a cerebellar haemangioma. The lesion was too small to be seen clinically (0.5 mm in diameter) and there was absence of dilatation of feeding vessels. It can be assumed therefore that patients with this syndrome can have subclinical retinal angiomas which are hard to detect even with careful biomicroscopy.

Jesberg et al. (1968) described three patients with the appearance of microangiomas in the retina where earlier careful examination had failed to reveal any vascular lesion. At this early stage it was observed that there was no dilatation of the vessels such as that seen with larger von Hippel tumours. They questioned the theory of congenital rests as a pre-requisite for the development of angiomas in the retina and decided that they developed in originally normal retinal blood vessels.

Goldberg & Duke (1968) studied histologically the retina from a patient with von Hippel-Lindau syndrome. They found hypertrophic and hyperplastic changes in the artery and vein leading to an early angioma. They concluded that the primary lesion is a malformation of the whole vascular complex of artery, capillaries and vein.

Case Reports

Case 1

Female born 1949. Mother was treated for angiomatosis retinae with photocoagulation in 1963 with a satisfactory result. The patient's four younger siblings were examined by an ophthalmologist and found to have normal eyes. There is no information concerning their relatives.

The patient was examined for the first time by an ophthalmologist at the age of 9 years because of poor sight in the right eye. The vision in the right eye was 0.1 and in the left eye 1.0. In the right eye there were vitreous opacities and peripapillary

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INCIPIENT LESIONS IN ANGIOMATOSIS RETINAE

BY

LOFTUR MAGNUSSON and RAGNAR TÖRNQUIST

Very little is known about the most early stages of retinal angiomatosis. In two patients with advanced angiomatosis in one eye incipient lesions were found in the other eye. The morphologic characteristics and the findings in fluorescein angiography are described.

Key words: retina - angiomatosis retinae - von Hippel's disease - incipient lesions - fluorescein angiography

At the turn of the century von Hippel described the clinical picture of angiomatosis retinae and in 1926 and 1927 Lindau published his observations on the association between the angiomas in the retina and cerebellum. At the same time he also drew attention to the occurrence of polycystic or angiomatous tumours in other organs. Subsequently many studies on the von Hippel-Lindau syndrome have been published and the pathogenesis and varied clinical pictures have been fairly well documented. The classical picture of a light red angiomatous tumour with large sinuous feeding blood vessels is well known and angiomatosis retinae with this appearance do not present a diagnostic problem. However the differential diagnosis may be difficult in earlier stages or when the disease is advanced and secondary changes dominate the appearance. Our primary interest has been in the earlier stages of angiomatosis retinae. We have found that by means of new methods of examination in

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Very little is known about the most early stages of retinal angiomatosis. In two patients with advanced angiomatosis in one eye incipient lesions were found in the other eye. The morphologic characteristics and the findings in fluorescein angiography are described.

Key words: retina - angiomatosis retinae - v Hippel's disease - incipient lesions - fluorescein angiography

At the turn of the century von Hippel described the clinical picture of angiomatosis retinae and in 1926 and 1927 Lindau published his observations on the association between the angiomas in the retina and cerebellum. At the same time he also drew attention to the occurrence of polycystic or angiomatous tumours in other organs. Subsequently many studies on the von Hippel-Lindau syndrome have been published and the pathogenesis and varied clinical pictures have been fairly well documented. The classical picture of a light red angiomatous tumour with large sinuous feeding blood vessels is well known and angiomatosis retinae with this appearance do not present a diagnostic problem. However the differential diagnosis may be difficult in earlier stages or when the disease is advanced and secondary changes dominate the appearance. Our primary interest has been in the earlier stages of angiomatosis retinae. We have found that by means of new methods of examination in

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atrophy with folds in the macula which accounted for the poor vision. It is not clear whether these changes had the same genesis as the changes which developed later in her eyes. On this occasion the fundus of the left eye was examined after dilatation and was found to be normal.

At the age of about 15 years she visited a doctor again because of deteriorating vision in the left eye over the previous six months. The vision in this eye had fallen to 0.3. At this time a typical von Hippel tumour was found temporal to the macula in the left eye, 3 x 3 disc diameters in size, with gross dilatation and tortuosity of the vessels between the disc and the tumour and early exudative changes in the retina. The patient was otherwise healthy.

Neurological examination including neuro-radiology showed no abnormal findings. Urography was normal. The angioma in the left eye was treated several times with photocoagulation according to Meyer-Schwickerath (1959) and also with trans-scleral diathermy. However, the result indicated that the lesion was too advanced to be treated effectively by these methods. The retina became detached and did not regress. Subsequently a cataract developed and the eye is now blind.

At the same time as the illness was diagnosed in the left eye, examination of the peripheral fundus of the right eye revealed small tortuous vessels and two small knots of vessels. These changes were followed for at least five years without any definite progression being observed.

At a routine examination in the autumn of 1971 it was observed that one of the knots of vessels had developed into a grey nodular formation with fine capillaries on the surface. A normal feeding artery and a somewhat tortuous vein were observed, however, no exudative changes were observed (Fig. 1).

Thus there had been clinical observation of progress from an uncharacteristic change in the early stages to an appearance more typical of angiomatosis retinae.

Case 2

Male, born 1945. No known familial eye disease. Previously healthy. In May 1970 there was sudden deterioration of vision of the left eye. Two weeks later he was examined by an ophthalmologist who diagnosed angiomatosis retinae of the left eye. He was admitted at once to the Eye Clinic. On admission the vision of the right eye was 1.0 (0.75) and in the left eye 0.1 (~2.5). In the left eye there was much retinal exudation and a typical von Hippel tumour situated below, near the equator and 5 disc diameters in size. In addition there were three small angiomas, one of which was situated on the disc.

Neurological examination was normal but the blood pressure was found to be high 140/110 mmHg. Bilateral carotid angiography and left vertebral angiography were performed and no abnormalities were found. However, renal angiography revealed expanded processes in both adrenal glands, the largest on the right side showing calcification centrally. Selective renal angiography confirmed these findings but the kidneys themselves appeared normal. In collaboration with the urologists the patient was admitted to the medical clinic for pre-operative assessment when he experienced the onset of headaches which were episodic and became increasingly severe. Repeated examinations of the catecholamines in the urine revealed rising levels which on the 19th November were noradrenaline 436 and adrenaline 89 µg/day, both considerably elevated. The blood pressure remained high. A short while later

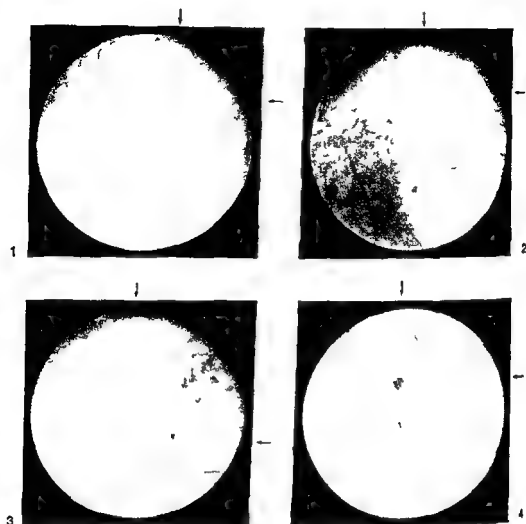


Fig 1

A typical angioma (Case 1) which was observed for several years as a dark red knot of vessels

Figs 2-4

Three angiomas at an early stage in the same eye (Case 2) These angiomas are at an earlier stage than is the one shown in Fig 1

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Thus there had been clinical observation of progress from an uncharacteristic change in the early stages to an appearance more typical of angiomatosis retinae.

Case 2

Male born 1949. No known familial eye disease. Previously healthy. In May 1970 there was sudden deterioration of vision of the left eye. Two weeks later he was examined by an ophthalmologist who diagnosed angiomatosis retinae of the left eye. He was admitted at once to the Eye Clinic. On admission the vision of the right eye was 1.0 (-0.75) and in the left eye 0.1 (-0.5). In the left eye there was much retinal exudation and a typical von Hippel tumour situated below near the equator and 1.5 disc diameters in size. In addition there were three small angiomas one of which was situated on the disc.

Neurological examination was normal but the blood pressure was found to be high 150/110 mmHg. Bilateral carotid angiography and left vertebral angiography were performed and no abnormalities were found. However renal angiography revealed expanded processes in both adrenal glands the largest on the right side showing a large centrally. Selective renal angiography confirmed these findings but the kidneys themselves appeared normal. In collaboration with the urologists the patient was admitted to the medical clinic for pre-operative assessment when he experienced the onset of headaches which were episodic and became increasingly severe. Repeated examinations of the catecholamines in the urine revealed rising values which on the 19th November were noradrenalin 456 and adrenalin 89 µg/day both considerably elevated. The blood pressure remained high. A short while later

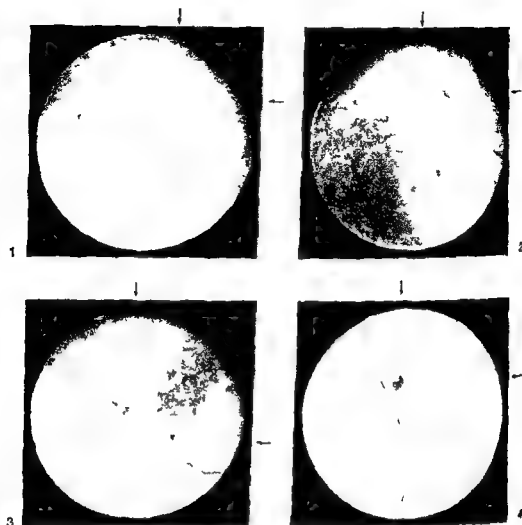


Fig. 1

A typical angioma (Case 1) which was observed for several years as a dark red knot of vessels

Figs. 2-4

Three angiomas at an early stage in the same eye (Case 2). These angiomas are at an earlier stage than is the one shown in Fig. 1

paralysis of the right oculomotor nerve and papilloedema in the right eye developed. In this critical state the patient was operated on first with a bilateral adrenalectomy and a few days later with removal of a cerebellar haemangioma situated on the right side of the cerebellum. Post operatively he has recovered well and has returned to his work in a bank.

During the first hospital visit in June 1970 photocoagulation treatment of the angiomas in the left eye was started. This was complemented with trans scleral cryotherapy over the largest angioma however no improvement was achieved. At the present time he has no useful vision in this eye.

Examination of the right eye on several occasions has revealed three rather small dark red spots which resemble retinal haemorrhages (Figs 11, 3 and 4). When these changes were examined carefully by biomicroscopy it was suspected that they might be early angiomas. Fluorescein angiography was performed and revealed that they were not haemorrhages but knots of blood vessels showing rapid transit of dye similar to arterio venous shunts (Fig. 5). One of these angiomas was treated with photocoagulation and healed completely.

Discussion

The cases described above have a number of features in common. The disease in one eye progressed to blindness emphasising the poor prognosis for the disease if treatment is not instituted at an early stage. In both patients the earliest changes were observed in the second eye and clinically these can be regarded as angiomatosis retinae. The differential diagnosis was at first somewhat uncertain. The genesis of the changes became apparent later in the first case the lesion progressed to a typical angioma and in the second case the answer was given by fluorescein angiography.

In these cases the early retinal angiomas had the following characteristics

1. The first change which can be detected clinically in angiomatosis retinae is a knot or conglomeration of dilated retinal capillaries without definite changes in the volume of the feeding artery or vein.

In the early stages the lesions have the same colour as normal blood vessels but as gliosis develops later the appearance of the angioma changes to a more nodular formation which is lighter in colour.

2. On fluorescein angiography leakage from the angioma is not found. This may explain the absence of exudation in the retina in the early stage. In addition one sees a rapid flow through the angioma indicating a lower capillary resistance than in the remainder of the capillary bed. The progressive dilatation of the feeding artery and vein may result from the increased blood flow through the angioma.

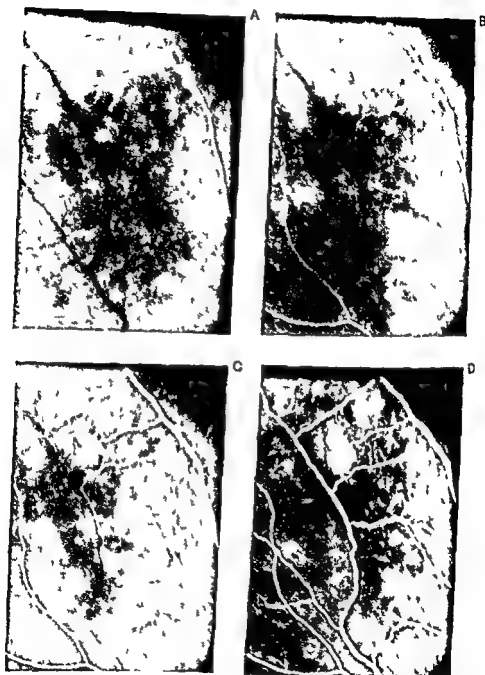


Fig 5

Fluorescein angiography of the angioma in Fig 4

A and B early arterial phase

C continuing the arterial phase peripherally the vein is empty of dye but the angioma is full of dye and centrally a lamination in the vein is clearly seen indicating more rapid transit through the angioma than in the capillary bed elsewhere - in other words an arterio venous shunt

D the arterio venous phase in which the vein is filled peripheral to the angioma

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SIDE EFFECTS OF VITAL STAINING WITH TETRAZOLIUM ALCIAN BLUE

BY

M S NORN

Vital staining of cornea and conjunctiva with a mixture of tetrazolium and alcian blue effected a permanent green colouring of connective tissue or precipitation of red crystals in 0.6% of 1375 eyes. This colouring subsided in the course of weeks or months.

Tattooing can be avoided by omitting vital staining with tetrazolium alcian blue in eyes with connective tissue left uncovered by epithelium (from corrosion or deep keratitis or resulting immediately after removal of sutures or during operation).

Key words: tattooing - side effects - connective tissue - vital staining - cornea - conjunctiva - tetrazolium - isodonitrotetrazolium - alcian blue

Vital staining of the cornea and the conjunctiva with new dyes can contribute towards giving additional information. For instance in 1962 I introduced alcian blue for staining conjunctival mucus and in 1971 isodonitrotetrazolium for staining damaged enzyme containing cells in the conjunctiva. Further

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Fig 1

Tattooing of a lime burned cornea stained by alcian blue half an hour after the accident By courtesy of Dr Frangoulis Thessaloniki Greece

About half an hour after the accident he was stained by alcian blue 0.5-1 % The stained area remained unchanged for 2½ months The visual acuity was 10/10 when the patient left the clinic

The patient has not yet been followed up further

In this case the connective tissue of the cornea and in spots that of the conjunctiva had become exposed and damaged with a consequent pronounced tattooing of the ground substance

Iodonitrotetrazolium in rare cases may precipitate as fine red crystal needles in exposed connective tissue

I observed tattooing after vital staining with alcian blue and/or tetrazolium in 10 out of 183 cases or 0.6 per cent



Fig 2

Case 1 Tattooing under the conjunctival lobe by tetrazolium alcian blue in a 54 year old man subjected to antiglaucomatous iridectomy Photo 13 months later

elucidation is obtainable by vital staining with the following mixture of the two dyes

iodonitrotetrazolium	100 mg
alcian blue	25 mg
phenylmercuric nitrate	0.1 mg
distilled water to	10 g
aseptically prepared	

So far I have vital stained 1 828 eyes of which 910 were with 1 % alcian blue 302 with 1 % iodonitrotetrazolium and 616 with a mixture of 1/4 % alcian blue and 1 % tetrazolium

The patients do not complain of smarting pain on instillation of these dyes. They do complain however with rose bengal which causes transitory smarting pain particularly in cases where the dye stains intensely (keratoconjunctivitis sicca).

The tetrazolium salts are *enzyme toxic substances* (Pearse). The drug firm Sigma therefore warns against "contact with skin and against breathing dust." This warning refers to the substance as such. I observed no irritation of mucus or skin by the aqueous 1 % solution used in the cases under review.

The number of substances suspected of *carcinogenic* action is increasing. Iodonitrotetrazolium is a nitrophenol compound, and thus is related to certain suspected carcinogens. However no references to carcinogenesis of iodonitrotetrazolium (Sigma) exist.

The theoretical risk of carcinogenesis by the compound is negligible when it is used for diagnostic purposes where the individual patient is exposed to only one or few doses (of about 0.1 mg each).

Tattooing

Alcian blue stains mucus. The ectodermal mucus is produced by goblet cells and accumulates into a mucous thread in the conjunctival fornix or round sutures for instance from which the vital stained mucus disappears again within a few hours.

Alcian blue can penetrate into the connective tissue and stain the mesodermal mucus of its ground substance. This staining may result in tattooing.

Such a pronounced discoloration is illustrated in Fig. 1 representing a case communicated to me by Dr. Frangoulis.

The case was one of a lime burn that had damaged the corneal epithelium.



Fig 1

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The patient has not yet been followed up further.

In this case the connective tissue of the cornea and in spots that of the conjunctiva had become exposed and damaged with a consequent pronounced tattooing of the ground substance.

Iodonitrotetrazolium in rare cases may precipitate as fine red crystal needles in exposed connective tissue.

I observed tattooing after vital staining with alcian blue and/or tetrazolium in 10 out of 18.7% cases or 0.6 per cent.



Fig

Case 1. Tattooing under the conjunctival lobe by tetrazolium alcian blue in a 54 year old man subjected to antiglaucomatous iridectomy. Photo 18 months later.

Case 1

A man aged 54 subjected to antiglaucomatous iridectomy (case no 910/0) had one drop of tetrazolium alcian blue instilled under the conjunctival lobe before the lobe was sutured. An area 8 mm in diameter was stained. Maximum staining (arbitrary grade 5) was still present the next day. Six days later the colour had faded somewhat (grade 3) and there were now found intensely stained green spots with few bright red crystals in two broad bands over the conjunctiva off the iridectomy. No oedema nor any signs of irritation.

Five months later the red crystals had totally disappeared and the green spots had grown paler (grade 2). After 15 months only one streak of fine green dots of the lowest colour grade was left over an area of 2 x 6 mm hardly visible with the naked eye (Fig. 2). In the slit lamp the dots were seen to be located in the connective tissue deep to the superficial thin conjunctival vessels above a few large vessels situated just in front of the sclera.

Case 2

During cataract extraction one drop of tetrazolium alcian blue was instilled below the conjunctival lobe (case no 954/70). Punctate green staining resulted but had faded appreciably after one week. No red granules were seen. The patient failed to appear for follow up examination.

Case 3

In an ante experiment with introduction into the inferior fornix of a cotton thread moistened with 5% silver nitrate vital staining with tetrazolium alcian blue was performed at the same time. A small green spot appeared indicating corrosion in the inferior fornix. The spot was no longer visible after 15 months.

Case 4

A patient with four marginal keratitis elements had vital staining performed. Four green spots occurred on the cornea at the sites of the four elements. In addition four spots appeared at the caruncle and medially on the inferior tarsus. Three weeks later the colour was paler. Eight months later only one minute spot persisted on the cornea and two likewise minute spots on the conjunctiva.

Case 5

Vital staining was performed the day after diathermic necrotizing of vessels in the limbus corneae. Deep green staining resulted. Two months later the colour had almost disappeared. No traces were left on follow up just over 12 months later.

Case 6

Staining with tetrazolium alcian blue resulted in an intense red colour and a paler green colour in a patient with central keratitis. Five days later only a minimum of red colour persisted. Follow up 15 months later no traces left.

Case 7

After cataract extraction (376/71) vital staining was performed immediately following removal of two corneoscleral sutures. The suture canals were stained intensely red and green. Three days later only a pale green colour persisted and it had totally disappeared after one week.

Case 8

After cataract extraction with corneal incision (755/69) vital staining was performed with tetrazolium on removal of the sutures. The suture canals assumed a red colour of maximum intensity being filled with red crystal needles. Twenty four hours later the colour had faded to grade 2. The colour was still recognizable four months later. At follow up three years later no traces were left.

Case 9

A marginal keratitis with ulcer was stained moderately by tetrazolium. The colour had totally disappeared after three months.

Case 10

A marginal keratitis was weakly stained by tetrazolium alcian blue. Three months later both the green and the red dye component had disappeared.

The most pronounced tattooing was noticed in the experimental studies (staining under conjunctival lobe staining of suture canal on removal of suture). Cosmetically disfiguring tattooing was seen in a small number of cases only and subsided in the course of a few months.

Discussion

The present investigation showed that vital staining with tetrazolium alcian blue involves certain risks: persistent tattooing may occur, the dyes may possibly cause irritation and there is perhaps a small risk of their being carcinogenic.

Tattooing can be avoided by observing the *contraindication* not to drop dye on connective tissue left uncovered by epithelium (deep corrosion, deep keratitis, open suture canals).

Advantages and disadvantages of this diagnostic procedure should be weighed. Unfortunately tetrazolium alcian blue vital staining cannot be replaced by safe vital staining with other dyes (e.g. rose bengal - fluorescein).

Case 1

A man aged 54 subjected to antiglaucomatous iridectomy (case no 910/0) had one drop of tetrazolium alcian blue instilled under the conjunctival lobe before the lobe was sutured. An area 6 mm in diameter was stained. Maximum staining (arbitrary grade 5) was still present the next day. Six days later the colour had faded some what (grade 3) and there were now found intensely stained green spots with few bright red crystals in two broad bands over the conjunctiva off the iridectomy. No oedema nor any signs of irritation.

Five months later the red crystals had totally disappeared and the green spots had grown paler (grade 2). After 18 months only one streak of fine green dots of the lowest colour grade was left over an area of 2×6 mm hardly visible with the naked eye (Fig. 2). In the slit lamp the dots were seen to be located in the connective tissue deep to the superficial thin conjunctival vessels above a few large vessels situated just in front of the sclera.

Case 2

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A patient with four marginal keratitis elements had vital staining performed. Four green spots occurred on the cornea at the sites of the four elements. In addition four spots appeared at the caruncle and medially on the inferior tarsus. Three weeks later the colour was paler. Eight months later only one minute spot persisted on the cornea and two likewise minute spots on the conjunctiva.

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Advantages and disadvantages of this diagnostic procedure should be weighed. Unfortunately tetrazolium alcian blue vital staining cannot be replaced by safe vital staining with other dyes (e.g. rose bengal - fluorescein).

Case 1

A man aged 54 subjected to antiglaucomatous iridectomy (case no 970/40) had one drop of tetrazolium alcian blue instilled under the conjunctival lobe before the lobe was sutured. An area 6 mm in diameter was stained. Maximum staining (arbitrary grade 5) was still present the next day. Six days later the colour had faded somewhat (grade 3) and there were now found intensely stained green spots with few bright red crystals in two broad bands over the conjunctiva off the iridectomy. No oedema nor any signs of irritation.

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PERILIMBAL SUCTION CUP TECHNIQUE COMBINED WITH TONOGRAPHY OR BULBAR PRESSURE TEST

BY

A P NESTEROV N B FEDOROVA and E R DEVLIKAMOVA

The aqueous humor production is suppressed during the perilimbal pressure cup technique. This effect can be diminished if the intraocular pressure prior to the test is decreased by tonography or bulbar pressure test. When such combined procedure was employed the suction cup technique showed a 1.5 fold increase of the values of aqueous inflow in 91 normal eyes and a 1.3 fold increase in 25 glaucomatous eyes. In another series of 245 normal eyes, 115 eyes with open angle glaucoma and 91 eyes with chronic closed angle glaucoma either suction cup test or combined technique was performed. The mean values of aqueous inflow were significantly greater if tonography or bulbar pressure technique was performed prior to the suction cup test.

Key words: glaucoma - aqueous dynamics - inflow - suction cup test - tonography - bulbar pressure test

Several techniques for measurement of the aqueous humor inflow in human eyes have been described (Goldmann 1950; Grant 1950; Langley & MacDonell 1951; Rensgren 1954; Sobanski, Swietliczko & Szosland 1951; Jones & Marshall 1954; Hilm 1965). In clinical practice however only tonography and perilimbal suction cup test are employed. Tonography provides useful information

because tetrazolium – alcian blue can give information on facts which cannot be disclosed by any other dyes (Norn)

Vital staining with tetrazolium alcian blue serves to clarify whether the conjunctiva is bacterially infected or is sterile. A predominantly red mucous thread in the inferior fornix indicates presence of neutrophilic leucocytes (inflammation) whereas a predominantly green mucous thread suggests sterility. The method may be indicated pre-operatively or in conjunctival affections prior to a possible antibiotic therapy.

A suspicion of simple chronic conjunctivitis can be supported by the finding of red tetrazolium stained dots on the inferior or the superior tarsal conjunctiva.

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The aqueous humor production is suppressed during the perilimbal pressure cup technique. This effect can be diminished if the intraocular pressure prior to the test is decreased by tonography or bulbar pressure test. When such combined procedure was employed the suction cup technique showed a 1.5 fold increase of the values of aqueous inflow in 91 normal eyes and a 3.3 fold increase in 25 glaucomatous eyes. In another series of 248 normal eyes, 113 eyes with open angle glaucoma and 91 eyes with chronic closed angle glaucoma either suction cup test or combined technique was performed. The mean values of aqueous inflow were significantly greater if tonography or bulbar pressure technique was performed prior to the suction cup test.

Key words: glaucoma - aqueous dynamics - inflow - suction cup test - tonography - bulbar pressure test

Several techniques for measurement of the aqueous humor inflow in human eyes have been described (Coldmann 1950; Grant 1950; Langley & MacDonald 1950; Rosengren 1950; Sobanski, Swietliczko & Szosland 1954; Jones & Maurice 1964; Holm 1968). In clinical practice, however, only tonography and perilimbal suction cup test are employed. Tonography provides useful information

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on the aqueous outflow facility. Unfortunately the errors in the measurement of the rate of flow are so great that it seems impossible to draw any certain conclusion in each particular case.

The perilimbal suction cup test was advanced by Rosengren (1934-1936) and further developed and studied in detail by Ericson (1958). Although this test can be used for estimation of the aqueous outflow facility (Rosengren 1936 Galin Baras & Mandell 1961) its major advantage as compared to tonography is the more valid measurement of the rate of aqueous inflow.

At the same time there is reason to believe that the rate of aqueous inflow has been underestimated by the suction cup technique. In fact when using this technique the mean value of aqueous inflow in normal eyes is only equal to 0.7-0.9 mm³/minute (Ericson 1958 Nesterov & Fedorova 1965). It is universally accepted that the rate of flow is about twice as much as the above figures (Goldmann 1955).

This difference can partially be explained both by the incomplete blockade of the aqueous pathways during the suction cup test and by the inaccuracy of the calibration table which is used for calculation of the ΔV value (Lingham 1963).

Another cause of the error in the measurement of the aqueous inflow by the suction cup technique is the decrease of the rate of aqueous production due to the rise of the intraocular pressure (Ericson 1958 Lingham 1963). To diminish the unfavorable action of this factor it seems reasonable to decrease the intraocular pressure just before the suction cup test is performed. This can be accomplished by tonography or by the bulbar pressure test.

The purpose of the present study is to compare the volume increments of the globe (ΔV) which have been obtained both by the suction cup test alone and by the combined technique.

Techniques

Perilimbal suction cup test (standard technique) The intraocular pressure was measured by the Schiotz electronic tonograph. The Ericson cup was then placed on the eye and the negative pressure of 50 mmHg was applied. After 15 min the cup was removed and the intraocular pressure was once again measured. Friedenwald's table (Friedenwald 1957) was used to calculate the volume increment of the globe.

Combined technique First either tonography or bulbar pressure test was performed. The technique of the bulbar pressure test has been described else

where (Nesterov Churbanova & Kolotkova 1973) Immediately after tonography or the bulbar pressure test the perilimbal suction cup test was performed as described above

Results

The aqueous inflow in 91 normal eyes of 80 persons and in 25 eyes with primary open angle glaucoma of 23 patients was studied by both the standard and the combined techniques In 58 of these eyes the standard technique was the first procedure On the next day at the very same time of the day the combined technique was performed In the other 58 eyes the inverse order of investigation was carried out

Results are given in Table I In each case the ΔV value after combined technique was greater than after the standard suction cup test The average difference between the ΔV values obtained by the two techniques were 5.3 mm³ in normal eyes ($P < 0.001$) and 2.17 mm³ in glaucomatous eyes ($P < 0.05$)

The results of another series of investigations are summarized in Table II This series includes 243 normal eyes of 201 persons 113 eyes of 95 patients with primary open angle glaucoma and 91 eyes of 74 patients with chronic closed angle glaucoma Only one procedure either standard suction cup test or the combined technique was performed in each case In all 278 eyes were examined by the standard suction cup test and the other 169 eyes were investigated by the combined technique

In each group of Table II the mean ΔV values obtained by the combined technique were significantly larger than those obtained by the suction cup test alone

Table I

Standard and combined suction cup techniques Results obtained in the same eye by both techniques

Suction cup technique	Normal eyes			Open angle glaucoma		
	No	ΔV (mm ³)		No	ΔV (mm ³)	
		Mean	SD		Mean	SD
Standard technique	91	10.9	2.41	25	6.0	3.23
Combined technique	91	16.2	3.57	23	8.2	3.29

Table II

Standard and combined suction cup techniques Results obtained in different eyes

Diagnosis	Standard technique			Combined techniques		
	No	IV (mm ²)		No	IV (mm ²)	
		Mean	SD		Mean	SD
Normal eyes	147	11.25	3.33	96	14.11	3.91
Eyes with open angle glaucoma						
(a) controlled	52	5.60	2.79	16	13.33	3.34
(b) uncontrolled	22	4.07	1.63	29	9.15	3.08
Eyes with closed angle glaucoma						
(a) controlled	39	6.62	3.12	18	13.11	3.23
(b) uncontrolled	18	4.05	1.92	16	9.15	2.0

Discussion

The data presented above indicate that a significant increase in the IV values occurs when tonography or bulbar pressure test had been performed prior to the suction cup test. When such a combined procedure was employed in one and the same eye the suction cup technique showed a 1.5 fold increase of the value of aqueous inflow in normal eyes and a 1.3 fold increase of this index in eyes with open angle glaucoma.

The following explanation of this effect seems to be reasonable. The aqueous production can be subdivided into pressure dependent and pressure independent portions (Barany 1963). The suction cup technique involves an increase of the intraocular pressure. The rise of the ocular tension is due to the deformation of the anterior part of the globe and to the continuous retention of the aqueous humor in the globe (Ericson 1958, Linnér, Swegmark & Tornquist 1962). The rise of the intraocular pressure leads to the decrease of the pressure dependent portion of the aqueous production and to the ejection of blood from the choroidal vessels (Ytteborg 1960, Fisher 1962). Both of these factors decrease the value of IV obtained by the suction cup technique.

In normal eyes both tonography and bulbar pressure test reduce the intraocular pressure by about 6 to 8 mmHg. In glaucomatous eyes the pressure drop

after outside compression of the globe depends on the facility of aqueous outflow and on the initial level of the intraocular pressure

The preparatory compression of the eyeball therefore diminishes the unfavorable action of the suction cup technique both on the aqueous humor production and on the intraocular blood volume

Combined suction cup technique proves to be a useful test for investigation of the aqueous humor dynamics. Tonography and bulbar pressure test may be employed for estimation of the aqueous outflow facility and the suction cup technique may be used for the measurement of the aqueous inflow

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HEREDITARY CENTRAL RETINAL ANGIOPATHY

BY

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A family with three members affected by a central retinal angiopathy is reported. The fundus changes consisted of tortuous arterioles, ectatic capillaries, microaneurysms, small retinal haemorrhages and tiny white dots. The changes were demonstrated by colour fluorescein angiography. The retinal changes simulate those described in hereditary haemorrhagic teleangiectasia (Rendu-Osler-Weber's disease) and in familial retinal arteriolar tortuosity, both showing dominant inheritance. Although none of the three patients had other stigmata of hereditary haemorrhagic teleangiectasia, it is proposed to consider the presently reported cases as well as those reported under the diagnosis of familial arteriolar tortuosity as a localized manifestation of a disorder which in other families may give the clinical picture of Rendu-Osler-Weber's disease.

Key word: colour fluorescein angiography - hereditary haemorrhagic teleangiectasia - familial arteriolar tortuosity - microaneurysms

In ophthalmoscopically visible central retinal angiopathy with aneurysms the cause almost invariably is diabetes mellitus. Certain other far less common cases can, however, give a similar fundus picture. Examples now classic are sickle cell anaemia, macroglobulinaemia, pulseless disease and retinal venous thrombosis.

The present paper reports a family with a central retinal angiopathy probably of dominant inheritance. Special attention is given to the possible

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were seen Nasally and above the right fovea three aneurysms several blurred red dots and a few tiny white spots were seen There were no exudates or neo vascularization Around the left fovea a few red dots and white spots and no exudates or neo vascularization were seen

Slit lamp examination with contact lens confirmed the above findings but showed in addition some small retinal haemorrhages and a sudden transition from the macular arterioles to the capillaries Numerous tiny white luminous degenerations or exudates were seen in the macular region No neo vascularization was seen and no changes in the peripheral fundus

Fluorescein angiography of the right eye (Fig 9) revealed very distinct vessels The perimacular vessels were irregular The capillaries close to the fovea were coarse and in a strange way mutually connected by irregularly running hairpin like anastomoses often with a knot like torsion in the middle There were large capillary free areas The sudden transition from arterioles to capillaries was evident The few large aneurysms continued to fluoresce and showed no leakage

A new examination (January 1979) still showed slightly reduced visual acuity The examination was totally unaltered except for the large macular aneurysms of the right eye There were now only two with different locations than a year earlier

Fluorescein angiography of the iris disclosed an incomplete ring of confluent points at the margin of the pupil There was no leakage of dye

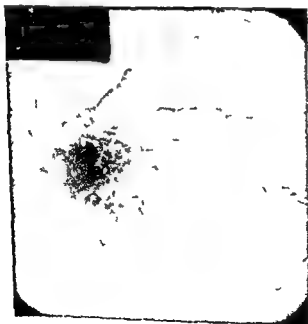


Fig 9

Colour fluorescein angiography of right macular area of case III 3 (March 19 71)

relationship to familial retinal arteriolar tortuosity (Beyer 1958, Werner & Gafner 1961, Cagianut & Werner 1968, Goldberg et al 1972) and familial haemorrhagic teleangiectasia (Rendu Osler-Weber's disease) François 1938, Massa et al 1966 and others).

FAMILY P

Fig. 1 comprises 17 members in four generations. Affected persons are reported below.

Case 1

(III 3) The proband was a 40 year old woman with slightly reduced visual acuity in both eyes. Ophthalmoscopic picture suggestive of diabetic retinopathy.

History. There were diabetes mellitus in the family of the father, who himself had this disease to a mild degree. At the age of 15 years the proband was examined for diabetes mellitus which was not found. The patient had a congenital hip luxation. During the last 3-4 years she had suffered from slight coughing, but otherwise she had had good health. There had been no frequent nose bleedings. The patient was attending this time because she had noted a slight bilateral reduction of visual acuity.

Ophthalmological examination (March 1971). Visual acuity in the right eye was 0.5 + 1.00 sph + 1.00 cyl 40° in the left eye 0.9 + 1.50 sph. External eyes and ocular motility were normal. At slit lamp examination the anterior segments of the eyes were normal except for a small subepithelial opacity below the center of the right cornea. There were no abnormalities in the conjunctival vessels or in the irides. Applanation tonometry showed 14 mmHg in both eyes.

Ophthalmoscopy showed normal discs. The arterioles were slightly tortuous, attenuated and of slightly varying diameter. The veins were normal except for some compression at the \times crossings. In the macular regions slight pigment disturbances.

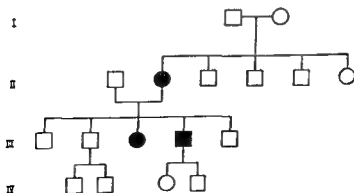


Fig. 1

Hereditary central retinal angiopathy (Family P)

DISCUSSION

The fundus picture with scattered red dots in the posterior pole might simulate a diabetic retinopathy (Kohner et al 1967). The aneurysms however were large and the perimacular arterioles slightly tortuous, dilated and often seen to terminate abruptly. The numerous tiny white refractile spots were also characteristic but their exact nature remains obscure. Neo vascularizations or definite exudates were not observed. The fluorescein angiographies substantiated the lesions and in addition demonstrated a network of coarse irregular capillaries surrounding avascular areas. These capillaries had a hairpin like course sometimes with a knot like torsion in the middle. The large aneurysms showed strong fluorescence throughout the length of the film and no signs of leakage.

The iris fluorescein angiographies showed peri pupillary vascular dilatations but no leakage. This lesion is known from diabetic iridopathy (Jensen & Lundbæk 1968; Baggesen 1969).

Changes similar to those of the present family are rare, apparently occurring only in hereditary haemorrhagic teleangiectasia (Rendu Osler Weber's disease) and in retinal arteriolar tortuosity.

Hereditary haemorrhagic teleangiectasia (R O W) is a vascular anomaly showing a familial autosomal dominant occurrence. Clinically it is characterized by haemorrhages and teleangiectasias. The latter are found in the skin and mucous membranes notably the nasal but may occur anywhere. Epistaxis is the most frequent single sign. The teleangiectasias may be of different types: stellate or nodular. The number of lesions may vary from a few to several hundreds. Pathogenetically various mesodermal dysplasias have been incriminated. Histopathologically the teleangiectasias are composed of neo vascularizations, dilated capillaries and thin walled vessels with degeneration in the elastic and muscular tissue. In addition changes in collagen and elastic fibres are seen.

The ocular manifestations are most commonly palpebral and conjunctival lesions (Massa et al 1966; Schulze & Tost 1966 and others). Conjunctival lesions may give rise to the dramatic sign of bloody tears.

Fundus lesions are rare in this disease. They comprise retinal haemorrhages (Cjessing 1916; François 1938; Serris 1948; Latour & Carrion 1945; Bonnet 1952; Inigo 1951; Lucendet & Magnenat 1953; Calmettes et al 1958; Massa et al 1966; Alaerts 1966). More specific lesions are dilated and tortuous veins (François 1938; Landau et al 1956; Massa et al 1966) and tortuous arterioles (François 1938; Massa et al 1966). Retinal teleangiectasias (Meyer-Schwickerath & von Barnewisch 1961; Davis & Smith 1961) localized arterio-venous aneu-

General examination The patient was found to be in good health except for her hip luxation. There were no teleangiectatic lesions in the skin or mucous membranes, especially the nasal mucosa.

Laboratory investigation Blood sugar analysis and repeated glucose loadings were normal. There was no sugar in the urine. Blood pressure was measured daily for prolonged periods and was never above 150 systolic and 110 diastolic. Chest roentgenogram normal except for a slightly large heart (diameter 14 cm thorax $24\frac{1}{2}$ cm). Electrocardiography was normal.

ESR 16 mm/h. haemoglobin 150 g/100 ml erythrocytes $4\frac{1}{2}$ and $44 \times 10^6/\mu\text{l}$ mean cell volume 91 and 94 μml mean cell haemoglobin concentration 35% and 35%, leucocytes $7.3 \times 10^3/\mu\text{l}$ differential counting normal serum sodium 144 mN potassium 4.5 mN total CO_2 25 mM calcium 10.5 mg% phosphorous 3.9 mg% (normal). Serum urea 33 mg% serum creatinine 1.0 and 0.9 mg% serum protein 6.7%. Diuresis never exceeded 1200 ml no protein glucose or erythrocytes in the urine.

Total serum lipids 822 mg% (normal) cholesterol 253 (normal) triglycerides 154 (normal) lipids in urine below 8 mg% (normal). Excretion in the urine of 1. keto steroids (11.4 mg/d) and ketogenic steroids (12.6 mg/d) was at the upper limit of the normal range. A skin biopsy was normal no lipid deposits. Histological diagnosis hypertrophy suggestive of sclerodermia.

Case 2

(II 2) 66 year old woman the mother of patient no. 1. Always of good health no eye symptoms in particular.

Ophthalmological examination (April 1941) Visual acuity in the right eye was $10 + 9.25$ sph + 0.50 100° in the left eye $10 + 3.00$ sph + 0.50 0°. Slit lamp examination including conjunctival and pericorneal vessels normal. Ophthalmoscopy showed normal discs. The arteries were attenuated the veins normal except for compression at the a-v crossings. In both central regions there were arteriolar ectasias and aneurysms similar to those seen in case 1. There were no exudates. The observations were verified by fluorescein angiography.

Case 3

(III 4) 38 year old man brother to patient no. 1. Previously of good health never any eye symptoms.

Ophthalmological examination (May 1941) Visual acuity in both eyes $10 + 1.50$ 00. Slit lamp examination normal except for several small infracentral subepithelial opacities in the left cornea. Fundus examination (ophthalmoscopy and 8 mirror contact lens of Goldmann) revealed normal discs thin arteries. In the right perimacular region several small aneurysms and a single ectatic arteriole with an abrupt termination were seen. In both macular regions there were several tiny white atrophic perivascular areas.

Remaining cases

Examination was performed on II 1, III 2, III 5, IV 1, IV 2 and IV 3. All had normal fundus examination.

III 1 died as newborn. II 1, 2, II 3, II 4, II 5 and IV 4 were not examined.

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rysms (Forker & Bean 1963) new formed vessels in the retina (Davis & Smith 1971) and on the disc (Roubin 1957) vitreous haemorrhage (Davis & Smith 1971) and exudates (François 1938 Cuendet & Magnenat 1953) have also been reported Other lesions are colloid degenerations (Cuendet & Magnenat 1953 Calmettes et al 1958) and choroidal ruptures (Massa et al 1966)

Retinal arteriolar tortuosity was first described as a familial lesion by Beyer (1958) in a father and son In addition to tortuous arterioles there were macular and paramacular haemorrhages and normal venules Both patients suffered from recurrent nosebleedings and the father had nasal telangiectasia but there were no other signs of hereditary haemorrhagic telangiectasia Werner & Cafner (1961) reported a father and three children with retinal arteriolar tortuosity and recurrent retinal haemorrhages During childhood the father had had haemorrhages over both tibias The father had hypogammaglobulinaemia which may be of some interest as retinal microaneurysms were reported by Frenkel & Russe (1967) in a patient with hypogammaglobulinaemia Cagianut & Werner (1968) reported four patients from a family with retinal arteriolar tortuosity and recurrent haemorrhages Venules were normal Fluorescein angiography showed no dye leakage Goldberg Pollack & Green (1972) reported a family with six cases of retinal tortuosity and haemorrhages four with tortuosity but no haemorrhages and one with haemorrhages but no tortuosity Fluorescein angiography in two cases revealed a few macular microaneurysms and in one case tiny refractile dots of unknown type were seen in the fovea

Similarities exist between the fundus changes in the cases of hereditary haemorrhagic telangiectasia those of retinal arteriolar tortuosity and the present family A dominant inheritance is probable There are fundus changes comprising tortuous and ectatic vessels retinal haemorrhages and aneurysms Fluorescein angiography has been performed in only a few of the cases and it therefore is not surprising that aneurysms are described only seldom No constant blood abnormalities are reported arterial hypertension occurred in some cases and was suspected in the present family The lesions seen in the three patients of our family fit into the pictures of both hereditary haemorrhagic telangiectasia and familial retinal arteriolar tortuosity It is known that localized lesions may occur in patients with hereditary haemorrhagic telangiectasia and the families studied by Beyer and by Werner & Cafner had some stigmata suggestive of this disease Rather than introducing a new disease occurring in one or a few families we therefore propose to consider all these cases as having manifestations of a mesodermal dysplasia which may in some families give rise to generalized haemorrhagic telangiectasia and in others present only as localized lesions

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CONJUNCTIVAL LYMPHOCYTOSIS AFTER CORNEAL TRANSPLANTATION

BY

NIELS EHLERS and STEEN AHRONS

Conjunctival lymphocytosis was followed after penetrating corneal transplantations. Examinations were made of scrapings taken with the spatula and stained according to May Grunwald Giemsa. In a series of 97 ABO compatible transplantations a semi quantitative correlation was found between the HLA compatibility and the degree of lymphocytosis in the second to fifth postoperative month. It is suggested that conjunctival lymphocytosis reflects immune processes in the cornea. Clinical use of the method could probably be made in the second or third month when strong lymphocytosis would contraindicate a reduction or indicate an initiation of immunosuppressive therapy.

Key words: corneal transplantation - graft rejection - conjunctival lymphocytosis - histocompatibility

Complications to corneal transplantations may be considered to be of an immunological nature unless other reasons are evident (French 1972). Designations as graft rejection or graft disease are used although in the individual case it may be difficult to prove that immune processes are active. Graft rejections do occur (Mauumenee 1961, Faure 1964) and it is now generally realized that the clinical picture with acute onset of visual disability and oedema in a previously clear and reactionless graft is an immunological phenomenon.

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Grunwald Giemsa The patients were followed clinically and scrapings made by one of the authors (N E) while the other (S A) performed the microscopical evaluation without any knowledge about the clinical course or the degree of histocompatibility between donor and recipient. The lymphocytosis was arbitrarily graded as - (+) + and ++.

Observations

The study comprised 27 patients: 22 ABO compatible, 5 ABO incompatible. The 22 ABO compatible cases are summarized in Table I. This group comprises according to the best HL A match: 4 C, 7 D, 5 E, 1 F and 5 G matches. The clinical diagnoses also are given in the table. As regards the results, 16 of the grafts were clear and six were opaque. One of these, the last one in the Table, later cleared up. This patient was reported in detail by Ehlers & Ahrons (1971a). The preoperative pathology, especially the presence of vessels in the cornea, probably influences the occurrence of lymphocytosis, the occurrence of graft rejection and the final result. The present material is too small to allow an exhaustive analysis. The five ABO incompatible transplantations made up a very inhomogenous group and will not be further commented on.

Within the first two months a varying degree of lymphocytosis was observed apparently irrespective of the HL A compatibility. In the later course the lymphocytosis occurred mainly among the less compatible transplantations as illustrated by the Table. It must be admitted, however, that even among the G matches a lymphocytic reaction may be missing (case BJ). The arrows in the diagram indicate graft rejections. In most cases with graft rejection the result was an opaque graft, but in four cases the graft finally became clear.

Discussion

The present study was undertaken in an attempt to elaborate a method which could be used in the postoperative period of corneal transplantations to indicate the occurrence of immune reactions. Conjunctival scrapings with a spatula were preferred to Norn's quantitative pipette method (Norn 1960, 1962) because of simplicity and because scrapings were recommended by Zucker & Basu (1968).

In a clinical series reported by Ehlers & Kissmeyer Nielsen (1972) there was a correlation between the result and the HL A compatibility. A series showing

nomenon The significance of rejection lines moving across the cornea has recently been stressed (Silverstein 1972) Measurement of corneal thickness may prove to be a suitable procedure in following an endothelial rejection

It is the purpose of the present communication to demonstrate that following human penetrating corneal transplantation the occurrence of lymphocytes in the conjunctival fluid reflects the immune processes in the cornea and this reaction may precede graft rejection

Methods

1 Surgical technique

Penetrating 7 or 7.1 mm corneal transplantations were performed under general anaesthesia The donor cornea was placed on wax and punched out from the endothelial side Sixteen to 18 interrupted virgin silk sutures were placed with the aid of a microscope and air was injected into the chamber On the first postoperative day the patient was examined with the slit lamp

Topical treatment with atropine steroids and chloramphenicol was given from the first postoperative day and from the fifth day systemic prednisone 30 mg The sutures were removed after 2-6 weeks The systemic prednisone was reduced from the 14th day to 15 mg This dose and the topical treatment were continued for several months

2 Compatibility testing

Histocompatibility between donor and recipient was investigated with the micro lymphocytotoxic technique (Kissmeyer Nielsen & Kjærbye 1967) and the HL A compatibility graded decreasingly from A to G (see Kissmeyer Nielsen & Thorsby 1970) Only when four HL A antigens are demonstrated can the match be graded with certainty and often therefore we can only indicate the "best" and the worst possible matches Between some HL A antigens cross reactions are found Incompatibilities for cross reactive antigens were disregarded when the best match grades were evaluated In addition the ABO type of donor and recipient was determined As regards corneal transplantation and histocompatibility reference is made to previous publications (Ehlers & Ahrons 1971a b Ehlers & Kissmeyer Nielsen 1972)

3 Conjunctival scrapings

Conjunctival smears were prepared with a blunt spatula as recommended by Zucker & Basu (1968) and after air drying were stained according to May

Grunwald Giemsa The patients were followed clinically and scrapings made by one of the authors (N E) while the other (S A) performed the microscopical evaluation without any knowledge about the clinical course or the degree of histocompatibility between donor and recipient. The lymphocytosis was arbitrarily graded as - (+) + and ++.

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Discussion

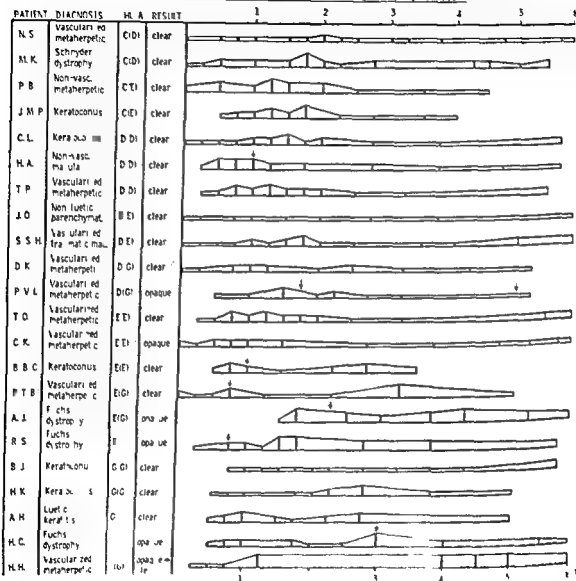
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Table I

The lymphocytosis graded from - to ++ is illustrated by the height of the bars. The arrows indicate clinical signs of rejection. The HLA match grade is given by letters C to G. The "worst possible" match is given in parentheses

CONJUNCTIVAL LYMPHOCYTOSIS AFTER CORNEAL TRANSPLANTATION



the same tendency was presented by Batchelor & Cases (1972). Assuming that the transplantations grouped as C and D matches are more compatible than those grouped as E, F and G, a stronger lymphocytosis should be expected in the latter group. Considering the second, third and fourth postoperative months this generally applies as is shown in Table I. We take this to be an indication

that the immune reactions in the cornea are influenced by the number of HL A incompatible antigens present in the transplant. This is supported by the observation that graft rejection occurred simultaneously with lymphocytosis. The only exception to this was the second rejection observed in case PVL. Occurrence of lymphocytes in the conjunctival fluid does not prove that passage through the tears is an important route in the immune reaction although as regards rejection of the epithelium this would not be surprising. The conjunctival lymphocytosis makes the strong effect of local steroid treatment understandable but of course gives no indication about a generalized sensitization and response.

Although the lymphocytosis probably reflects immune reactions this method has been found to be clinically time consuming and difficult to administer. The microscopic examinations in the present series were made independently of the clinical course. The number of cells in a conjunctival scraping is generally small and a regular differential counting is not possible. Therefore it is to be suspected that knowledge about the clinical situation would bias the evaluation of the cytology. The method cannot be generally recommended for the follow up of corneal transplantation but a study of conjunctival cytology may be useful in the late course of corneal transplant on where a strong lymphocytosis would contraindicate a reduction or indicate the initiation of immunosuppressive therapy.

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MEASUREMENTS OF THE EPISCLERAL VENOUS PRESSURE BY MEANS OF AN AIR JET

BY

C E T KRAKAU J WIDAKOWICH and K WILKE

A method for determination of the venous pressure in the conjunctival and episcleral vessels is described. The external pressure needed for the vessels to collapse is achieved by means of a stream of air directed against the vessel. As the eye is untouched by the instrument local anaesthetics usually are not needed. The method is fast and easy to perform. The measurements indicate that the pressure of the aqueous conveying episcleral veins often is 3-4 mmHg higher than that of the conjunctival veins.

Key words: venous pressure - air jet - ocular tension - glaucoma - aqueous dynamics

The episcleral venous pressure is an important factor in the calculation of aqueous dynamics. Principally two kinds of devices have been used for measuring it. The pressure chamber (Seidel 1923) has one side covered by a thin membrane which is pressed to the conjunctiva. The pressure inside the chamber is raised until the conjunctival vessels collapse. The torsion balance (Oldmann 1951) has a small well defined surface which is pressed against a

vessel and the weight needed for compression is read. Pressure values of about 10 mmHg have been found in episcleral veins and about 1 mmHg higher in aqueous veins (Linnér 1955). An extensive table of the measurements by a number of authors is found in Podos (1968). Brubaker (1967) compared the pressure chamber and the torsion balance on rabbits and found a well reproducible obliteration point in the pressure chamber. The mean values did not differ significantly from those obtained by direct cannulation. The torsion balance method was less satisfactory because of difficulty in estimating the point of collapse.

A different approach was taken by Stepanik (1969) who measured the episcleral venous pressure indirectly via the intraocular pressure after compression of the bulb.

The aim of the present study is to describe a new method in which the external pressure is applied by means of a stream of air. It has the advantage of permitting a free inspection of the area under pressure.

A stream of air has been used in ophthalmological methods previously by Boberg Ans (1952) who investigated it as a means of quantifying the blinking reflex. More recently it has been applied to intraocular pressure measurements (Amer Optical Co. Southbridge Mass.).

Apparatus

The simple apparatus is drawn schematically in Fig. 1. A diaphragm pump of the type used for aeration of aquarium produces a stream of air. After being somewhat moistened in a water flash (W) the air passes through a needle valve (NV) by means of which the flow volume is regulated. After a branching off for a water manometer (M) the stream is directed to a solenoid operated valve (SV). When this valve is in its normal position the stream is directed through a variable resistance (R) into free air. In position for measurement it is let out through a mouthpiece (O) 0.5 mm in diameter. The outlet (R) is adjusted to the same resistance as the mouthpiece, i.e. the reading of the manometer is unaltered when the solenoid valve changes its position. The mouthpiece is fixed to the slit lamp microscope between the axes of the two tubes and ends 3 mm in front of the eye when the conjunctiva is in focus (Fig. 2).

The place where the centre of the air stream hits the eye is adjusted to correspond with a hair cross in one of the eyepieces of the microscope.

The air jet directed against the eye is felt mainly as a tickling in the ciliae. This sensation is reduced if the temperature of the stream approximates that of the body. To this end a heating wire is placed around the last part of the tube and warms the air to 35–37°C. The unpleasantness is then usually so slight that local anaesthesia is not necessary.

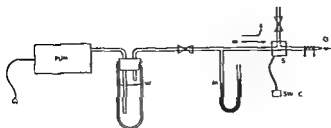


Fig 1

A schematic drawing of the apparatus W water bottle NV needle valve M water manometer SV solenoid operated valve H heating wire O mouthpiece 0.5 mm in diameter R variable resistance n normal passage for the air stream m the air stream directed to the mouthpiece

The air is moistened to some extent by letting it pass through the water bottle (W). A higher degree of saturation might be desirable in order to avoid drying of the conjunctiva but this has been found unsuitable since drops of water may then condense in the narrow air passages.



Fig 2

Part of the instrument mounted on a slit lamp H heating wire O mouthpiece A adjusting screw

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The flow was adjusted to a manometer reading on (M) of 20 cm aq which corresponds to a flow of 500 ml/min. The tube was about 10 mm in diameter at the point where the manometer M was connected (say point 1) so the contribution of the kinetic energy term was small. The stagnation point pressure reached 17-18 cm aq axially in front of the orifice (Fig. 3). The difference ($p_1 - p$) is attributed to a flow resistance of the air in the thin tube. The viscosity can obviously be neglected as it is only a rough approximation. We note in Fig. 3 that the axial pressure remains fairly constant in the axial part of the stream and drops rapidly outside the central jet. With a narrower Pitot tube the demarcation of the jet would have been even more distinct.

When the conjunctiva is hit by the stream of air a small hollow is formed after a few seconds because the subconjunctival fluid is pressed aside.

Thus there is a non zero pressure gradient parallel to the surface of the conjunctiva but as the velocity of tissue fluid is comparatively small we may consider the pressure constant in the small volume of tissue embedding the vessel in focus.

Measurements also were made with a flat surface surrounding the Pitot tube at the same level as its orifice. There were no significant changes in the pressure values of the central stream.

The relation of manometer (M) pressure to axial pressure at 3 mm distance from the mouthpiece is shown in Fig. 4.

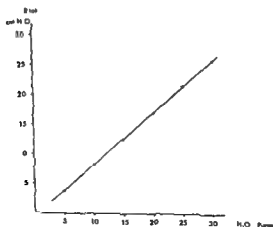


Fig. 4

The relation between manometer pressure and the air stream pressure 3 mm from the mouthpiece

Calibration

For an incompressible fluid the relation between pressure and velocity is expressed by Bernoulli's law provided the fluid is ideal i.e. without viscosity. Thus if the lateral pressure p and the velocity v are measured at two points (1) and (2) on a tube with a variable bore we have

$$P_1 + \rho \frac{v_1^2}{2} = P_2 + \rho \frac{v_2^2}{2} = \text{const}$$

where ρ is the density of the fluid

This rule is also applicable to gases if subsonic velocities are treated

The Pitot meter is a tube in which the tip points in the direction of the flow. The flow of liquid is dammed up immediately before the tip. In the centre of the dammed-up region there is a "stagnation point", where the fluid comes to a standstill ($v_s = 0$). The pressure at this point is called the total pressure and

$$P_s = \rho \frac{v_1^2}{2} + P_1$$

In a thin tube with smooth walls the flow of air can be considered free of turbulence. If the tube has an open end the air leaves the opening as a jet which remains practically unaffected by turbulence for some distance depending on the dimensions of the mouthpiece and the velocity of the air in the tube.

The distribution of pressure in front of the mouthpiece has been mapped by means of a Pitot tube with its opening directed against the air stream. A hypodermic needle with an inner bore of 0.3 mm was used as a Pitot tube. It was connected to a water manometer. The orifice of the Pitot tube was placed at a distance of 1 to 5 mm from the outlet of the air stream and at various distances from the axis of the stream.

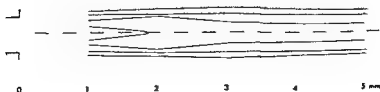


Fig 3

The pressure in front of the mouthpiece. The 4, 8, 16 and 18 cm H_2O isobars have been measured by a Pitot tube 1-5 mm from the mouthpiece opening. The water manometer was set at 20 cm H_2O .

width +++ total obstruction of the vessel and the blood stream is seemingly cut off. However, even in this stage careful inspection of the vessel proximally to the collapsed area shows streaming blood corpuscles or aggregations. A complete standstill of the corpuscles requires a further pressure rise of 2-6 cm H₂O reckoned from +++ point. This point is useful for measurements on aqueous veins where it is difficult to use the + ++ +++ grading but where an admixture of blood cells is generally seen.

Repeated measurements were made in two groups of vessels: 1) superficial and subconjunctival veins; 2) episcleral deep veins receiving an aqueous vein. (Only this type of vein has been referred to as 'episcleral' in this study.) The measurements were made on the same vessel every time in each group. When the same subject was used in more than one group, different vessels may have been used in different groups.

I. REPEATED MEASUREMENTS ON CONJUNCTIVAL VEINS

a) The same vessel on the same occasion

On three women aged 25-32 the points + ++ +++ were estimated seven times on the same occasion. As seen in Table I the mean for + varied from 7.3 to 8.9 mmHg, for ++ from 9.4 to 10.8 mmHg and for +++ from 12.0 to 13.1 mmHg.

b) The same vessel on different occasions

On six healthy women aged 20-32 one daily series of measurements was made for six days. The mean values for the end points of each individual are shown in Table II. The + level varied between 7.4 and 9.4 mmHg, the ++ level between 9.3 and 11.7 mmHg and the +++ level between 12.0 and 14.9 mmHg.

Table I
Conjunctival veins

Subject	A		B		C	
	Mean	s.d.	Mean	s.d.	Mean	s.d.
	5	0.78	8.9	0.78	7.6	0.47
	9.4	0.66	10.8	0.41	9.8	0.56
	12.0	0.60	13.1	0.63	12.8	0.60

Series of measurements in each subject on the same occasion

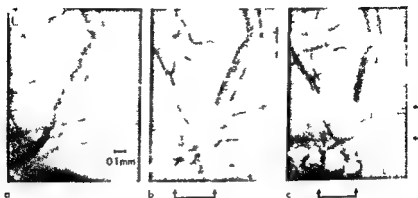


Fig 5

a) conjunctival vessels b) the air stream directed against a large vessel and the blood stream reduced to about half its width ++ c) total obstruction of the vein +++ The arrows denote the area of effect of the air stream The white areas in b and c are reflexes from the delli caused by the air pressure

Operation

A vein on the surface of the eye ball is chosen and adjusted to the cross of the eyepiece. A 25 to 40 fold magnification is used. The air stream is released by pressing the button operating the valve (SV) and its effect on the vessel is observed (Fig 5). Only a few seconds of blowing are necessary and it is desirable to keep this period as short as possible in order to avoid drying the conjunctiva. For the same reason the patient is requested to blink occasionally.

Two different modes of measurement have been applied. In one of them the manometer pressure is kept constant during the observation of the vessel. It is changed in steps of 1-2 cm of water and the effect at each pressure level is noted.

In the second mode the needle valve was opened slowly by a small motor started simultaneously with the air jet. When the external pressure reaches a sufficient height the blood vessel collapses. The pressure increase and the air stream are then stopped by releasing the press button and the manometer pressure is read.

Results

It has been found convenient to use a grading of the effect of the air stream similar to that used by Brubaker (1967): 0 no effect + slight deformation of the vessel ++ clear effect with reduction of the blood stream to about half its

II REPEATED MEASUREMENTS ON EPISCLERAL VEINS

a) The same vessel on the same occasion

The measurements were made on each of four healthy women. The fixation of the experimentees often takes a somewhat uncomfortable direction when the aqueous transporting episcleral veins are inspected. This made a fast procedure desirable and therefore only the point ++ was measured in this series. The mean values were found to range from 14.3 to 20.1 mmHg (Table III) as compared to the mean values of approximately 13 mmHg seen in Tables I and II.

b) The same vessel on different occasions

On three subjects one daily series of measurements was made for three days. The values from the measurements are shown in Fig. 6. The mean value for + was 11.1 for ++ 14.1 and for +++ 16.1 mmHg.

III COMPARATIVE MEASUREMENTS ON EPISCLERAL AND CONJUNCTIVAL VEINS ON THE SAME SUBJECT

As there seemed to be a higher pressure in episcleral veins measurements were made on both episcleral and conjunctival veins on the same occasion in three subjects. As seen in Table IV the pressure in the episcleral veins was between 2.6 and 4 mmHg higher than in the conjunctival veins. Also the intraocular pressure was measured with the applanation tonometer in these patients and found to be in the vicinity of the ++ level.

A few series were also made with the second mode of measurement i.e. with a continuous increase of the external pressure during the observation of the vessels. The values obtained by this procedure did not differ significantly from those of the stepwise measurements.

Table III
Episcleral veins. The same vessel on the same occasion

Subject	K	C	L	M
Number of measurements	10	10	10	10
Mean () mmHg	14.6	18.0	20.1	14.3
sd	0.66	1.03	0.81	0.84

Table II
 Conjunctival veins Measurements on the same vein on different days

Subject	D	E	F	G	H	I	Group				
Number of measurements	6	6	6	6	6	6	36				
	Mean	s d	Mean	s d	Mean	s d	Mean				
+	81	0.81	74	0.44	79	0.59	85	0.63	90	1.12	84
++	101	0.45	93	0.86	117	0.99	100	0.72	102	0.56	104
+++	132	0.91	120	1.26	149	2.1	128	1.13	124	0.44	131

Table IV
Episcleral and conjunctival veins

Subject	M		L		A	
	Ep	Conj	Ep	Conj	Ep	Conj
+	99	68	104	98	104	98
++	130	83	149	119	136	111
+++	153	111	174	136	162	136
IOP	14		14		16	

pressure in the vessel can be expected to fall somewhere within this range but we need a more definite determination. Since the blood velocity in the small conjunctival vessels is very small the total pressure (p_t in eq. 2) and the lateral pressure (p_l in eq. 1) do not differ by more than a fraction of a mmHg and no ambiguity results from simply talking of the pressure.

It was frequently observed that with increasing pressure of the air jet the blood stream narrows. This cannot be attributed to some kind of separation of the corpuscles from the plasma since sometimes the walls of the narrowing vessels are seen well enough. If the vessels had been made of a flaccid inelastic material a less dense though wider blood stream would have been expected. The reduction of the vessel diameter at this stage can hardly be due to an active contraction of the vessel since it narrows immediately when the air jet is turned on and recovers its width at once when the pressure is released.

It is presumed then that the constriction is an effect of the elastic forces of the wall which balance the transmural pressure difference. The contraction should continue until this difference is zero. If we proceed beyond the point of equal pressure inside and outside the vessel the latter collapses and flattens. By a further increase of pressure the blood flow can be brought to a complete standstill and the pressure read at this point must be higher than the intra vascular pressure.

At the first of our points of effect on the vessel denoted by + we are probably below the vascular pressure the deformation or constriction of the vessel at this point being slight. At the point +++ i.e. flattening of the vessel or at the point of standstill of the corpuscles the pressure applied is no doubt too high. The point ++ where a considerable diameter reduction is noted corresponds best with values generally given for the episcleral venous pressure and also for the theoretical reasons discussed it is likely that we should find the best estimate at this somewhat imprecise point.

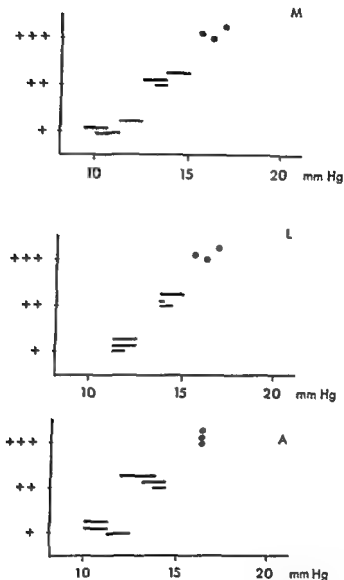


Fig 6

Daily series of measurements of the same episcleral vein in three subjects during three days. A point represents the lowest pressure with +++ effect. The effects of + and ++ are seen in a range of pressure and noted by a line. The series of the first day has its symbols lowest in the groups.

Discussion

As a rule there is a slight deformation of the conjunctival vessel when the pressure of the air stream is about 8 mmHg and a complete collapse and stand still of the blood corpuscles in the vessels at about 15 mmHg. Presumably the

Table IV
Episcleral and conjunctival veins

Subject	M		L		A	
	Ep	Conj	Ep	Conj	Ep	Conj
+	9.9	6.8	12.4	9.8	10.4	9.8
++	13.0	8.3	14.9	11.2	13.6	11.1
+++	15.3	11.1	17.4	13.6	16.0	13.6
IOP	14		14		16	

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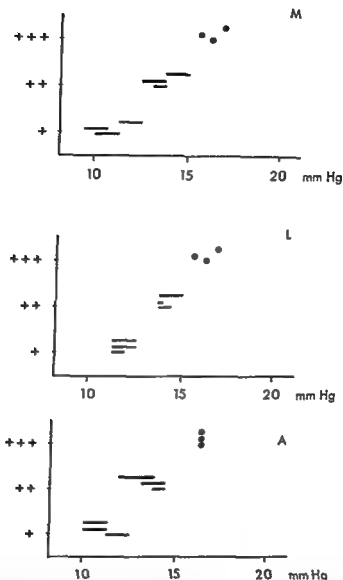


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BY

ERIK LINNÉR

The four factors applanating force applanated area intraocular pressure and displaced intraocular volume were measured simultaneously and independently in enucleated human eyes. The experiments were carried out at constant intraocular pressure.

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Key words: applanation - corneal applanation - displaced intraocular volume - Imbert-Fick law

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When repeated measurements are made some hyperaemia is generally seen in the area exposed to the air stream. The measurements in Table I consist of seven consecutive series 30 secs apart. No trend towards lower or higher pressure readings was observed during these measurements. It seems probable that the measurements do not appreciably influence the pressure inside the vessels.

Comparing the points of equal effects in the series reported in Tables I-IV we note that the pressure of the aqueous conveying episcleral veins is 3-4 mmHg higher than that of the conjunctival ones. This effect cannot be attributed to the fact that the episcleral veins are situated more deeply in the conjunctiva since the lower pressure is found in both superficial and deep conjunctival veins.

In studies on the outflow of aqueous the praxis is often adopted to make the venous pressure constant at about 10 mmHg. Our findings indicate that this may not always be justified. Since already a small deviation of the pressure from this value may have considerable influence on the calculations further investigations into this important question seem desirable.

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For obvious reasons it is not possible to measure the intraocular pressure routinely by introducing a needle into living human eyes. Different indirect methods producing a deformation of the eyeball by a known force have been developed. The applanation tonometry as developed by Goldmann is considered to be the most accurate method of measuring the intraocular pressure in human eyes. It is based on the Imbert Fick law which can be written as follows $A = W/P$

A is the area of applanation, W the applanating force and P the intraocular pressure. This law is valid only if the membrane is perfectly dry, thin, elastic and flexible. However, the cornea does not meet these requirements. In developing the applanation tonometry Goldmann found that the bending force required to flatten the cornea and the surface tension exerted by the tear film tended to cancel each other out when the diameter of the applanated area was about 3 mm. By choosing an area with a diameter of 3.06 mm the simple relationship according to the Imbert-Fick law could be applied.

Various factors related to the intraocular pressure such as ocular rigidity and the dynamics of aqueous humour and blood in the living human eye are of great importance from physiological and clinical points of view. It is therefore of interest to explore how far applanation surfaces larger than 3 mm in diameter can be used.

Furthermore, changes in the shape of the eyeball during applanation are not necessarily limited to the corneal applanation. Especially at larger areas of applanation and when heavier weights are used, additional changes in the anterior as well as in the posterior part of the globe might play a role which should be taken into consideration when calculating volumes of displaced intraocular fluid.

Various attempts were made by this author about ten years ago to flatten large corneal areas by means of a pressure chamber where one side was closed with a soft membrane which could be brought into contact with the cornea. The determination of the shape of the membrane by optical means was not accurate enough, however, and the project had to be abandoned.

Recently the problem was reconsidered by Linnér & Thorburn (1971). Instead of registering the shape of the membrane, the position of its centre in relation to the surrounding reference surface was measured by means of a displacement transducer. This solution of the problem was found to give sufficient accuracy for measuring the applanating force at constant and known intraocular pressure in living human eyes.

The four factors: applanating force, intraocular pressure, applanated area and displaced intraocular volume are impossible to measure directly in the living human eye. It was felt that more data concerning the relationship

between these four factors could be of interest. The present study was therefore arranged so that all of these four factors could be determined simultaneously and independently in intact enucleated human eyes. In order to avoid distension of the eyeball when the intraocular pressure was changed by placing a weight on or removing it from the eye, the experiments were carried out at constant intraocular pressure.

Materials and Methods

Eight human eyes enucleated not more than 48 hours previously were used. In order to keep the anterior segment free during the experiment, the intraocular space was connected to the instruments through the optic nerve. A syringe with a big needle (= 18G) was inserted into the vitreous through the optic nerve. By injection and withdrawal repeated many times, the vitreous could be partially replaced by physiological saline. In three experiments reported separately, the vitreous was flushed by a solution containing hyaluronidase. Two needles (= 18G) glued together with epoxy were then inserted through the optic nerve into the vitreous, and the optic nerve was sealed by a tight encircling suture. The eyeball was gently placed in a vertical position on a soft copper sponge which was supported by a wooden holder with a 20 mm diameter circular hole. The optic nerve with the two needles protruded through a slit in the sponge. One needle was connected through a polyethylene tube to a Sanborn pressure transducer. The other needle was connected in the same way to a servo controlled infusion/withdrawal pump (Model 600-900S, Harvard Apparatus Co. Inc., Dover, Massachusetts) modified to record infused volume. The intraocular pressure and the rate of infusion or withdrawal were continuously recorded on a Hewlett Packard 350 Series Recorder.

The force producing an applanated contact surface with the cornea was applied by placing a cap with a plane transparent surface on the cornea. Great care was taken to keep the cap free from any other support except the cornea. The weight of the cap alone was 2.60 g. By adding metal rings to the cap, the weight was increased stepwise to 5.56, 8.51, 11.51, 14.49 and 17.39 g. The outline of the contact surface was made clearly visible by adding a drop of India ink to the surface of the cap before it was placed in its position on the cornea.

A Canon camera was mounted in a vertical position above the eye. Under the light from two floodlights, pictures of the contact surface outlined by the black ring of India ink were taken with high contrast copy panchromatic film (Kodak

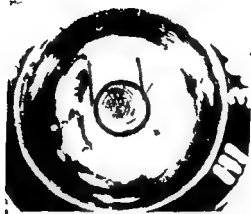


Fig 1

The applanated contact surface between the cornea and the cap outlined by a black ring of India ink. The magnification was determined by means of the distance between the two engraved black lines.

HC 135) Enlargements at about $7\times$ were made. The diameter of the contact surface was measured by means of a caliper under a Luxo magnifier. Furthermore, the distance between two black lines engraved on the inner surface of the cap was measured in order to determine the magnification on the enlarged pictures (Fig 1).

The experimental procedure was as follows. Care was taken to ensure that both needles into the eye were free and that the eyeball was supported in its vertical position only by the soft topper sponge. The cornea was kept moist.

The intraocular pressure was adjusted to constant and known levels varying between 15 and 40 mmHg. For each pressure level the different loads were placed on or removed from the eye in subsequent order. The displaced volume which was needed to bring the pressure back to its pre-set level within a few seconds was measured and a picture of the applanated area was taken (Fig 2).

Evaluation of the Methods

The weights placed directly on the eye were considered to be determined with sufficient accuracy as long as the weight was resting freely on the cornea without any other support. The measurements of the applanated surface were also accepted as being sufficiently accurate.

Direct measurements of displaced intraocular volume could be made two

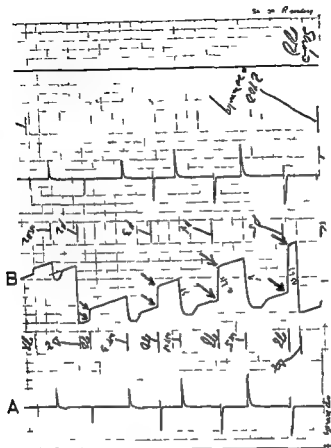


Fig 4

Tracing A shows the intraocular pressure kept on a constant level 15 mmHg. Tracing B demonstrates the volume changes. The arrows indicate the volume infused by the servo controlled infusion withdrawal pump when the weight was removed from the eye.

ways by withdrawal of intraocular fluid when the intraocular pressure had been elevated by placing a weight on the cornea or by injecting fluid into the eye when the pressure had been lowered by removing the weight from the cornea. In spite of all possible precautions taken to keep the connection between the servo system and the eye free at least a partial obstruction of the needle could not always be entirely excluded especially during withdrawal of fluid from the eye. From this point of view injection of fluid from the servo system into the eye was considered to be more reliable. Thus volume measurements when the weight was removed from the eye were the only ones used.

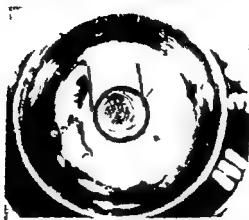


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Table I

The relationship between applanated area in mm² (A) force in grams (W) and intraocular pressure in mmHg (P) is expressed as follows $A = \bar{a} + m W/P$ The fitting of the regression line m indicated by the coefficient of determination (r^2)

Eye no	b	m	r^2	n
1	1.18	66.98	0.997	12
2	3.97	60.10	0.991	24
3	-0.35	67.33	0.997	27
5	-0.31	55.19	0.986	30
Mean	+0.45	62.91		
4 h	5.39	98.95	0.781	22
7 h	-0.22	64.51	0.990	14
8 h	-0.27	56.45	0.982	29

Hyaluronic
disc

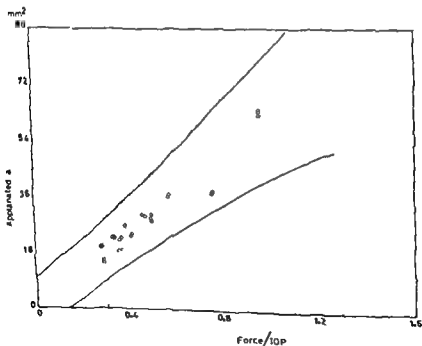


Fig 3

The relationship between force/intraocular pressure and applanated area in human eyes nos 1, 2, 3 and 5. The 95% prediction interval is indicated.

The most difficult problem was ascertaining that the passage through the second needle connected to the pressure transducer was completely free during the whole experimental procedure. There was no direct way to detect immediately whether a partial obstruction of the connecting needle or tube occurred during an experiment. The possibilities of erroneous pressure values were therefore carefully considered when the results were evaluated.

The main group consisted of six enucleated eyes. In two experiments there was reason to believe that the connection to the pressure transducer was at least partially obstructed. These two eyes were therefore not accepted for calculations including intraocular pressure values. When one of these experiments was repeated after flushing the needles thoroughly with a solution of hyaluronidase the connection could be kept open. The results from this and two additional eyes flushed with a solution of hyaluronidase are reported separately.

Results

Relationship between force (W) intraocular pressure (P) and applanated area (A) or displaced intraocular fluid (V)

Acceptable measurements were obtained in four enucleated human eyes. The relationship between applanating force (W) intraocular pressure (P) and applanated area (A) according to Imbert Fick law is demonstrated in Table I and in Fig. 3. The expression is as follows:

$$A = 0.45 + 62.21 W/P \quad (1)$$

A varied between 3.31 and 95.88 mm². W between 2.60 and 17.39 g and P between 15 and 35 mmHg. The fitting of the regression line is very good as indicated by the high coefficient of determination (r^2) for each eye separately. The intercept is close to zero. The slope of the regression line is lower than expected from Imbert Fick law. The scatter of b and m between individual eyes is relatively large. The slope of the regression line varies among the four

* The calculations of this as well as of all the following results were made according to Morrisson (1964). For each one of the four eyes ρ and η were estimated in the equation $A = 0.45 + 62.21 W/P$. By means of the 95% confidence ellipsoid for ρ and η the maximum and minimum A values for different W/P values were calculated. The 95% confidence interval for a mean value of V at any given value of A was thereby estimated (Fig. 5). Furthermore a 95% prediction interval for one new observation of A at a given W/P value was estimated.

Applanation and Displaced Intraocular Volumes

Table 1

The relationship between applanated area in mm² (A) force in grams (W) and intra ocular pressure in mmHg (P) is expressed as follows $A = b + m W/P$ The fitting of the regression line is indicated by the coefficient of determination (r^2)

Eye no	b	m	r^2	n
1	1.18	66.98	0.997	19
2	3.27	60.10	0.991	24
3	-2.35	67.33	0.997	22
5	-0.31	55.19	0.986	30
Mean	+0.45	60.91		
4 h	5.33	98.95	0.781	27
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Hyaluronic
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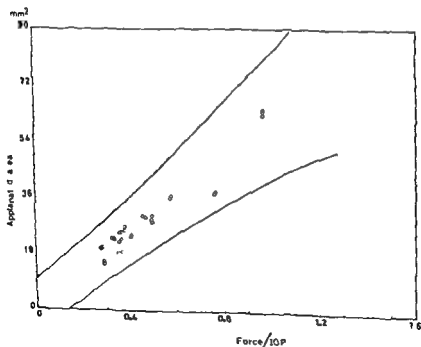


Fig 3

The relation b p between force/intraocular pressure and applanated area in human eyes nos 1 2 3 and 5 The 95 % prediction interval is indicated.

eyes. Thus a model of covariance cannot be used. It is not possible to decide clearly to what extent these variations are due to experimental errors or to differences among the eyes.

Three additional experiments were not considered to be directly comparable because the eyes were treated in a different way by flushing the vitreous with a solution of hyaluronidase before introducing the two needles through the optic nerve. The results are therefore reported separately in Table I but are not included in the Eq. 1.

The relationship between applanating force (W), intraocular pressure (P) and displaced intraocular fluid (V) (Fig. 4) can be expressed as follows:

$$V = -1.60 + 19.48 (W/P) + 40.48 (W/P)^2 \quad (?)$$

The experimental findings for each eye separately are given in Table II. The fitting of the regression line is very good as indicated by the high coefficient of determination (r^2).

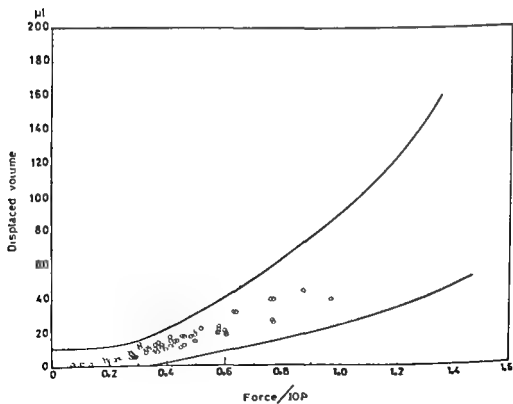


Fig. 4

The relationship between force, intraocular pressure and displaced intraocular volume in human eyes nos. 1, 3 and 5. The 95% prediction interval is indicated.

Table II

The relationship between displaced volume in mm³ (V) force in grams (W) and intraocular pressure in mmHg (P) expressed as follows $V = b + m(W/I) + c(W/P)^2$ The fitting of the regression line is indicated by the coefficient of determination (r)

Eye no	b	m	c	r	n
1	-1.43	21.22	38.94	0.998	1°
2	-3.30	23.90	39.01	0.986	24
3	-1.66	22.61	47.90	0.990	2°
5	+0.05	10.12	36.07	0.997	30
Mean	-1.60	19.43	40.43		

Relationship between applanated area and displaced intraocular fluid

Acceptable measurements were obtained in six eyes. The relationship between the diameter of the applanated area to the fourth (D⁴) and the displaced volume (V) for the same six eyes gave the following equation

$$V = 3.81 + 84.37 D^4 \quad (3)$$

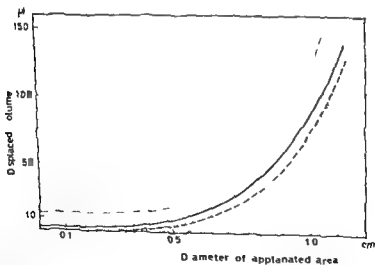


Fig. 5

The relationship between the diameter of the applanated area and the displaced intraocular volume in human eyes nos 1° 3 4 5 and 6. The mean value is indicated by a full line, the 95% confidence interval by thin dotted lines and the 95% prediction interval by thick dashed lines. The displaced volume calculated as an applanated spherical segment of the cornea is indicated by a thick broken line.

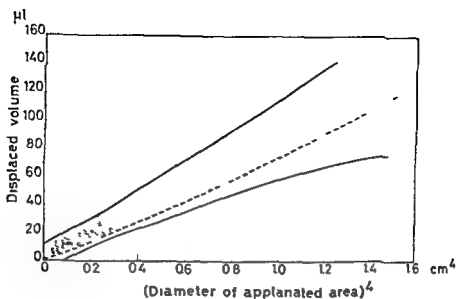


Fig 6

The same values as in Fig 5 recalculated to another scale on the abscissa showing the relationship between the fourth power of the diameter of the applanated area and the displaced intraocular volume in human eyes nos 1 2 3 4 5 and III. The fourth power of the diameter of the applanated area calculated as spherical segment is indicated by a broken line. The 95% prediction interval is indicated by full lines.

The relationship between the diameter of the applanated area and the displaced intraocular volume is not linear (Fig 5). For comparative purposes values of displaced volumes are also calculated as spherical segments for a radius of corneal curvature of 7.8 mm. The volumes calculated as spherical segments were found to be consistently smaller than those found experimentally on intact enucleated eyes and were close to the lower limit of the 95% confidence interval.

The experimental findings for each eye separately are demonstrated in Table III. A plot of all the results with a 95% confidence interval is given in Fig 6. The displaced volume calculated as an applanated spherical segment of the cornea (thick broken line) shows consistently lower values than the experimental findings.

The linearity of the regression line is very good, as indicated for each eye separately by the high coefficient of determination (r).

Three additional experiments were not considered to be directly comparable because the eyes were treated in a different way, in that the vitreous was

Applanation and Displaced Intraocular Volumes

Table III

The relationship between displaced volume in mm³ (V) and the fourth power of the diameter in cm of applanated area (D⁴) expressed as follows $V = b m D^4$. The fitting of the regression line is indicated by the coefficient of determination (r^2)

Eye no	b	m	r^2	n
1	3.16	75.11	0.999	19
2	1.06	97.32	0.998	24
3	7.03	89.17	0.999	27
4	2.96	74.89	0.993	19
5	2.41	90.66	0.985	30
6	5.66	84.07	0.973	19
Mean	3.81	84.37		
4 h	1.83	98.99	0.966	14
7 h	4.71	96.59	0.988	22
8 h	2.49	87.10	0.985	29

Hyaluronase

flushed with a solution of hyaluronidase before the two needles were introduced through the optic nerve. The results are therefore reported separately in Table III but are not included in the equation.

Discussion

Goldmann & Schmidt (1961) studied freshly enucleated human eyes and reported a good agreement between applanation tonometry and the intraocular pressure measured manometrically when the diameter of the applanated area varied from 5.06 to 7.0 mm.

In this study there was found to be a linear relationship between applanated area (A), force (W) and intraocular pressure (P). The expression was $A = 0.45 + 62.21 W/P$ as compared with the relationship $A = 73.5 W/P$ expected from Imbert-Fick law. The experimental finding of a slope not as great as expected indicates that the applanated areas are smaller than expected. This discrepancy is in agreement with the assumption that the applanating force is partly used as a force required to bend the corneal tissue. Gloster & Perkins using excised human corneas clamped in a perspex chamber reported similar results (1963).

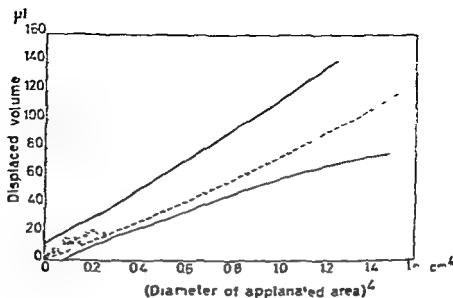


Fig 6

The same values as in Fig 5 recalculated to another scale on the abscissa show the relationship between the fourth power of the diameter of the applanated area and displaced intraocular volume in human eyes nos. 1, 2, 3, 4, 5 and 6. The fourth power of the diameter of the applanated area calculated as spherical segment is indicated by a broken line. The 95% prediction interval is indicated by full lines.

The relationship between the diameter of the applanated area and displaced intraocular volume is not linear (Fig 5). For comparative purposes values of displaced volumes are also calculated as spherical segments for a radius of corneal curvature of 7.5 mm. The volumes calculated as spherical segments were found to be consistently smaller than those found experimentally on intact enucleated eyes and were close to the lower limit of the 95% confidence interval.

The experimental findings for each eye separately are demonstrated in Table III. A plot of all the results with a 95% confidence interval is given in Fig 6. The displaced volume calculated as an applanated spherical segment of the cornea (thick broken line) shows consistently lower values than the experimental findings.

The linearity of the regression line is very good as indicated for each eye separately by the high coefficient of determination r^2 .

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Table III

The relationship between displaced volume in mm³ (V) and the fourth power of the diameter in cm of applanated area (D⁴) expressed as follows $V = b m D^4$. The fitting of the regression line is indicated by the coefficient of determination (r^2)

Eye no	b	m	r^2	n
1	3.16	75.11	0.992	12
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5	2.41	90.66	0.985	30
6	5.66	84.07	0.977	19
Mean	3.81	81.37		
4 h	1.83	93.99	0.966	14
7 h	4.71	96.32	0.938	22
8 h	2.49	87.70	0.955	29

Hyaluronidase

flushed with a solution of hyaluronidase before the two needles were introduced through the optic nerve. The results are therefore reported separately in Table III but are not included in the equation.

Discussion

Goldmann & Schmidt (1961) studied freshly enucleated human eyes and reported a good agreement between applanation tonometry and the intraocular pressure measured manometrically when the diameter of the applanated area varied from 3.00 to 7.0 mm.

In this study there was found to be a linear relationship between applanated area (A), force (W) and intraocular pressure (P). The expression was $A = 0.45 + 67.91 W/P$ as compared to the relationship $A = 73.5 W/P$ expected from Imbert-Fick law. The experimental finding of a slope not as great as expected indicates that the applanated areas are smaller than expected. This discrepancy is in agreement with the assumption that the appplanating force is partly used as a force required to bend the corneal tissue. Gloster & Perkins using excised human corneas clamped in a perspex chamber reported similar results (1963).

For calibration of the Filatov half tonometer Nesterov & Vurgaft (1972) examined 10 enucleated human eyes. An analysis after recalculation of their results ($n = 95$) according to Imbert Fick law showed a relationship between area (A) force (W) and pressure (P) as follows

$$A = 4.75 + 68.11 W/P \quad (4)$$

The relationship was found to be approximately linear for applanated areas varying between about 7 and 63 mm². The slope of the line was only slightly lower than would be expected on the basis of the Imbert Fick law.

All these experimental findings indicate to some extent a tendency to underestimate the applanated area.

The displaced intraocular volumes measured directly by means of an infusion pump were found to be larger than would be expected from the corneal applanation alone calculated as spherical segments.

These findings were in agreement with other findings based on enucleated human eyes. Moses, after studying the Mackay Marg tonometer, reported a displaced volume 17% larger than the volume estimated from the spherical segment (Moses 1966).

Stepanik & Ossoinig (1968) produced a 7 mm diameter applanation and increased thereby the intraocular pressure. During this procedure they measured the sagittal axis of the human eyeball *in vivo* by ultrasonic echograms. They could not confirm the assumption of a flattening of the posterior pole when the cornea was applanated. They concluded that instead of flattening of the posterior pole the aqueous may be displaced outwards towards the periphery of the anterior chamber and some deformation of the eye by the oblique muscles may take place.

In addition to the corneal deformation caused by the Schiotz tonometer resting on the eye, a possible deformation of the posterior segment of the globe has been considered by various authors (Friedenwald 1947, Becker & Friedenwald 1953, Goldmann 1959 and Priot & Weekers 1959).

On the other hand Gloster & Perkins (1963) used excised human corneas and found that the displaced volumes were in general agreement with the values calculated as spherical segments.

The experimental finding of a displaced intraocular volume exceeding the volume calculated as spherical segment might be of interest for the situation in the living eye. To my knowledge no direct measurement of the intraocular volume displaced by applanation in the living human eye is available.

It is possible that the deformation of the eyeball during applanation is different when the intraocular pressure is raised as compared to the deformation taking place when the intraocular pressure is kept constant. The experiments

in this study were carried out at constant pressure and the findings are therefore limited to this condition. In addition to the corneal applanation it seems reasonable to assume that some deformation of the anterior and/or posterior part of the globe might take place also in the living eye. Especially at larger areas of applanation the limbal area might be changed. Possible deformation of the posterior segment of the globe is probably smaller when the eye has its natural support in the orbit than when it is enucleated and rests on some soft layer. Another factor which might be of importance is the shape of the globe. A shortening of the sagittal axis of the eyeball is not going to give the same volume displacement in a spherical eye as in a myopic eye with a long sagittal axis. The shape of the myopic eye might be more spherical during applanation and the result might even be an increase of the intraocular volume.

The best conclusion concerning the displaced volume in the living human eye seems to be as follows. The volume calculated as a spherical segment represents a minimum value and the experimentally measured volume represents a maximum value of displaced volume.

If applanating force and intraocular pressure but not the applanated area are measured directly (Linnér & Thorburn 1971) the displaced intraocular volume can be estimated by means of these two factors according to Eq 2 (Table II and Fig 4) without including estimated values of applanated areas.

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KLINIK UND ULTRASTRUKTUR DER ZENTRALEN SCHEIBE BEIM SOGENANNTEN EXFOLIATIONSSYNDROM

VON

O BENEDIKT W GÜTTINGER und L AUBÖCK

Eine klinische Untersuchung von 1 1 Augen mit sogenanntem Exfoliations-
syndrom ergab in 90% das Vorhandensein einer zentralen Scheibe als
Teilaspekt dieser Erkrankung. Bisher konnte die klinisch oft sehr deutliche
Veränderung histologisch entweder nicht dargestellt werden oder es wur-
den Strukturen beschrieben, die dem Spaltlampenbild nur unvollkommen
entsprachen. Raster- und transmissionselektronenmikroskopische Unter-
suchungen an 4 Kataraktlinsen mit Kapselabschulferung sicherten nunmehr
die Existenz einer zentralen Lamelle von charakteristischem Aufbau als
morphologisches Substrat für die klinisch schon lange bekannte zentrale
Scheibe.

Key words: pseudoexfoliation - fibrillogenesis epithelialis - central
disk in pseudoexfoliation - electronmicroscopy - scanning electronmicro-
scopy.

Ola Sunde (1956) kam in seiner umfangreichen Arbeit über die so ge-
nannte Exfoliation der Linsen kapsel auf Grund eigener histologischer Unter-
suchungen zur Auffassung, dass die Wahrnehmung einer zentralen Scheibe als
Teilaspekt der bekannten Veränderungen bei dieser Erkrankung (Abb. 1) auf
einer optischen Täuschung beruhen könne. Weder O. A. Sunde noch Bertelsen

Eingegangen 4. Januar 1973

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An diesen Augen konnten wir im Bereich der zentralen Anteile der vorderen Linsenkapsel folgende wesentliche biomikroskopische Befunde erheben. Die Grösse der zentralen Scheibe entspricht ungefähr dem mittleren Pupillendurchmesser. Bei der Betrachtung an der lichtstarken Spaltlampe sind daher die äusseren Grenzen nicht erkennbar und eine Erweiterung der Pupille für eine genaue Beurteilung unbedingt nötig. Sowohl die Grösse als auch die Form der zentralen Scheibe können sich ändern. Dabei sind aber nur Änderungen möglich, die zu einer Verkleinerung ihrer Fläche führen. So folgt die Form der zentralen Scheibe operationsbedingten Pupillenänderungen und ihr Durchmesser nimmt nach Gaben von Miotika ab. Das klinische Erscheinungsbild wechselt stark und reicht von einer gerade erkennbaren homogenen Opaleszenz bis zu milchigweissen Membranen mit deutlichen oft aufgeworfenen Rändern. Diese starker ausgeprägten Scheiben lassen meist eine gleichmässige staubformige Strukturierung erkennen. Im allgemeinen ist das Ausmass der zentralen Veränderungen mit den bekannten übrigen Veränderungen der vorderen Augenabschnitte korreliert, gelegentlich ist aber bei einem sehr ausgeprägten peripheren Band eine kaum sichtbare zentrale Scheibe vorhanden. Dies ist besonders bei tiefer Vorderkammer und posteriorer Position der Linse der Fall. Voraussetzungen, die für die Ausbildung des sogenannten Schmalbandtyps der Linsenkapselabschilferung (Cifford 1957) verantwortlich zu machen sind. Am Rand der Scheibe findet man häufig polymorphe weisse Gebilde, diese sind wie zarte weissblaue Flockchen und Pigmentgranula, gelegentlich auch auf den zentralen Anteilen nachweisbar. Steht die zentrale Scheibe noch durch Brücken mit der peripheren granularen Zone in Verbindung, so kann man manchmal erkennen, wie die granularen Veränderungen nicht nur peripher, sondern auch zentral in Form gleichmässiger zungenförmiger Ausläufer enden.

Im Hinblick auf die Pathogenese der Erkrankung bedeutsame Beobachtungen konnten wir in 2 Fällen machen. In der Gegend der sogenannten intermediären klaren Zone fanden sich nur einige ovale umschriebene Stellen, die sich wie Lücken von der übrigen zart grau erscheinenden Umgebung abhoben. Die peripheren Abschnitte zeigten dabei keine deutliche Granulierung, sodass zentrale und periphere Veränderungen optisch kaum zu unterscheiden waren. In einem Fall konnten wir beobachten, wie diese Lücken sich innerhalb von Jahren zur intermediären Zone ausweiteten und dabei eine Granulierung der Peripherie einsetzte. Im anderen Fall fand sich im Partnerauge ein voll ausgeprägtes Exfoliationssyndrom, sodass man auch hier annehmen kann, dass die Entwicklung von den oben beschriebenen Veränderungen bis zum Vollbild einer sogenannten Kapselabschilferung ablaufen kann.

Sehr ähnliche Fälle teilte Gifford (1957) mit, der besonders auf die langdauernde Entwicklung bis zur Ausbildung einer zentralen Scheibe hinwies.

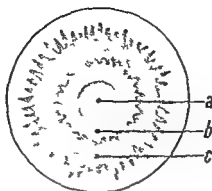


Abb 1

Schematische Darstellung der Veränderungen der vorderen Linsenkapself bei der sogenannten Kapselabschilferung

a zentrale Scheibe b intermediäre Zone c periphere granulare Zone

Drablös und Flood (1964) konnten bei ihren licht und elektronenmikroskopischen Studien morphologische Strukturen darstellen die diesen bei Spaltlampenuntersuchungen oft sehr deutlich sichtbaren Veränderungen entsprachen hätten Ashton und Mitarbeiter (1965) sowie Horven (1966) fanden nur vereinzelt stehende zarte granuläre und fibrilläre Substanzen auf einer normalen Kapsel ein Befund der sich nur schwer mit dem klinischen Bild der zentralen Scheibe vereinbaren lässt Da trotz zahlreicher licht und elektronenmikroskopischer sowie histochemischer Arbeiten die Pathogenese des sogenannten Exfoliationssyndroms nicht eindeutig geklärt ist erschien es uns von Bedeutung diesem Teilproblem sowohl durch klinische Beobachtungen als auch durch elektronenmikroskopische Untersuchungen nachzugehen

Klinische Untersuchungen

Alle während der letzten 5 Jahre diagnostizierten Fälle von sogenannter Kapselabschilferung wurden vereinzelt auch über Jahre mit einer Spaltlampe der Type Haag Streit 900 bei 16 und 24 facher Vergrößerung beobachtet Zur Wahrnehmung der oft sehr zart ausgeprägten zentralen Veränderungen ist ein möglichst schräger Lichteinfall wesentlich denn nur auf diese Weise lassen sich die oft geringgradigen Unterschiede zwischen der zentralen Scheibe und der sie umgebenden intermediären Zone erkennen 114 von 126 klinisch genau untersuchten Augen mit Kapselabschilferung wiesen eine zentrale Scheibe auf



Abb. 8

Zentrale Scheibe. Der Rand ist teilweise abgehoben und gegen die Mitte zu eingerollt.
Rasterelektronenmikroskopische Aufnahme C/Au bedampft Originalvergrößerung
6900

strukturell deutlich unterscheidbares Band mit einer durchschnittlichen Breite von $1,5 \mu$. Es besteht aus groben Fibrillen mit einer Dicke von etwa $280-360 \text{ \AA}$, die an geeigneten Stellen eine periodische Substanzverdichtung erkennen lassen und aus zarten, nicht so gut charakterisierbaren Fibrillen (Abb. 9). Die Filamente sind in eine feingranulare Grundsubstanz eingelagert. Dieses Band geht allmählich in die normale wolkige oder feingranular strukturierte Linsenkapsel über, die in dieser Gegend – ebenso wie die Linsenzellen – keine Besonderheiten zeigt.

Im Bereich der Intermediärzone (Abb. 8b) fehlt dieses Band entweder vollkommen oder es findet sich nur eine dünne Lage grober Fibrillen. An einzelnen Stellen sitzen dieser Kapsel busch- oder baumchenartig geformte Gebilde auf.

Ultrastrukturelle Untersuchungen

Untersuchungsmaterial und Methode 4 Kataraktlinsen die eine deutliche Kapselfabschilferung mit Ausbildung einer zentralen Scheibe gezeigt hatten wurden mit einem dünnen Kryostift ohne enzymatische Zonulolyse extrahiert unmittelbar *postoperativ* in 5 %igem phosphatgepufferten Glutaraldehyd *fixiert* und anschliessend orientiert zerteilt Die weitere Fixierung wurde teils in 1 %iger Veronalacetat gepufferten Osmiumsäure (nach Palade) teils in 1 %iger phosphatgepufferten Osmiumsäure (nach Millonig) durch 2 Stunden durchgeführt Nach Entwässerung in einer aufsteigenden Alkoholreihe erfolgte die Einbettung der für die histologische bzw elektronenmikroskopischen Untersuchung vorgesehenen Anteile der Linsen in Epon 812 Die Dünnschnitte wurden mit dem Ultramikrotom Om U2 der Fa Reichert gewonnen und mit Uranylacetat und Phosphorwolframsäure nachkontrastiert Die transmissionselektronenmikroskopischen Aufnahmen erfolgten mit einem Philips EM 200 Zur Durchführung der rasterelektronenmikroskopischen Aufnahmen wurden 2 Linsenhalften mit Gold bedampft und mit einem Stereoscan der Firma Cambridge Instrument Co Ltd (Mark II a) untersucht Auf diese Weise war an den selben Linsen eine Gegenüberstellung des Oberflächenbildes und des Durchstrahlungsbildes möglich

Ergebnisse

Rasterelektronenmikroskopie Die Abb 2 zeigt den etwas umgekrempelten Rand einer zentralen Scheibe Man erkennt deutlich die Niveaudifferenz zwischen dem am linken Bildrand gelegenen Anteil der Scheibe und dem am rechten Bildrand gelegenen Anteil der intermediären Zone Auch die Oberflächenstruktur beider Anteile ist deutlich verschieden Die zentrale Scheibe zeigt bei entsprechender Vergrösserung eine grobe unregelmässige hockerige Oberfläche und erscheint ähnlich einem Konglomeratgestein aus kugeligen und ovoiden Elementen zusammengesetzt (Abb 3) Die intermediäre Zone ist wesentlich feiner gekornt (Abb 4) und mit verschiedenen gestalteten Teilchen übersät die sich oft walzen- oder rollenformig darstellen Auf der Abbildung 5 kann man erkennen dass sich die zentrale Scheibe wie eine Lamelle ablosen lässt Die Oberflächenstruktur der darunterliegenden Linsenkapsel (Abb 6) ist deutlich von der Oberfläche einer normalen zentralen Linsenvorderfläche (Abb 7) unterschieden

Transmissionselektronenmikroskopie Die entsprechenden Durchstrahlungsbilder (Abb 8a) zeigen ein von der darunter gelegenen Linsenkapsel (Breite 23 μ)

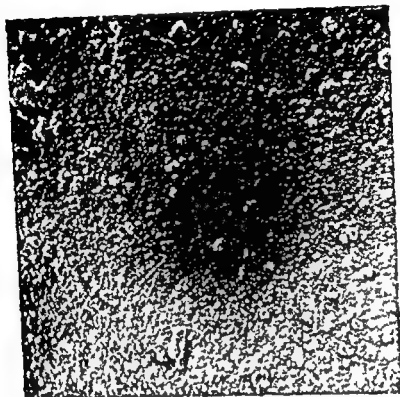


Abb. 4

Oberflächenstruktur der intermediären Zone Rasterelektronenmikroskopische Aufnahme
C/Au bedampft Originalvergrößerung 13 500 \times

rungen an Linsen mit sogenannter Exfoliation nachgewiesen werden. Die von Vogt (1983), Rehsteiner (1929) und Landolt (1957) mitgeteilten Befunde wie Vakuolenbildung, Langastreifung, Lamellierung und sogenannte Blätterteigstruktur der Kapsel, die der letztgenannte Autor vor allem zentral gefunden hatte, dürften Kunstprodukte sein, wie dies schon Busacca (1930) und Sunde (1961) vermuteten, da weder die genannten Autoren noch wir derartige Veränderungen nachweisen konnten. Unsere Untersuchungen ergeben eindeutig, dass das ganze Gebiet der zentralen Scheibe strukturell verändert ist und sich in der Oberflächenbeschaffenheit von den angrenzenden Zonen deutlich unterscheidet. Die Hautchennatur der Scheibe geht aus entsprechenden rasterelektronenmikroskopischen Befunden eindeutig hervor. Entfernt man diese Lamelle, tritt nicht die normale Linsenoberfläche zu Tage, sondern eine ebenfalls patho-

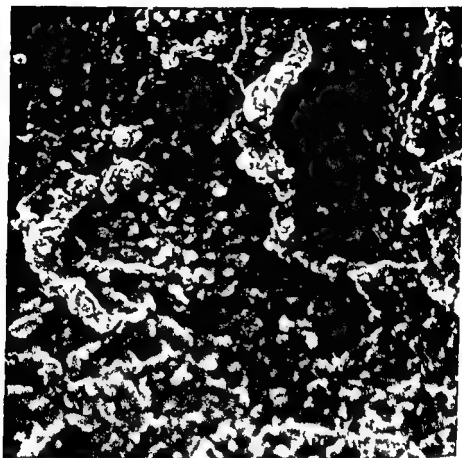


Abb 3

Oberflächenstruktur der zentralen Scheibe Rasterelektronenmikroskopische Aufnahme
C/Au bedampft Originalvergrößerung 13 500 x

(Abb 10) die ebenfalls aus den vorhin beschriebenen groben und feinen Fibrillen aufgebaut sind Dieses Material wurde bereits lichtmikroskopisch von Busacca (1928) und elektronenmikroskopisch von Blackstad und Mitarbeitern (1960) Bertelsen und Mitarbeitern (1964) sowie Ashton und Mitarbeitern (1965) genau beschrieben und bildet auch das morphologische Substrat für das an den verschiedenen Stellen der vorderen Augenabschnitte auftretende sogenannte Exfoliationsmaterial

Besprechung

Obwohl die zentrale Scheibe klinisch deutlich in Erscheinung tritt konnten bisher keine dem klinischen Aspekt entsprechenden histologischen Verände

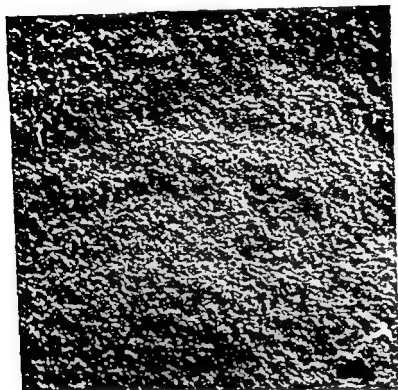


Abb 6

Oberflächenstruktur der künstlich von der zentralen Scheibe gelösten Linsenkapsel
Rasterelektronenmikroskopische Aufnahme C/Au bedampft Originalvergrößerung
10 500 \times

Die von uns erhobenen morphologischen Befunde lassen zwei Erklärungen zu

1) Es handelt sich um den Niederschlag einer an anderer Stelle produzierten Substanz, die sich im Bereich der Pupille in Form einer Scheibe einer normalen Linsenkapsel anlagert. In anderen Zonen dagegen durch bestimmte mechanische Belastungen morphologisch modifiziert wird.

2) Die Scheibe entsteht im Rahmen eines pathologischen Prozesses aus einer normalen Struktur der vorderen Linsenkapsel. Die Veränderungen der angrenzenden Zonen können dann ebenfalls aus den verschiedenartigen Beanspruchungen der Linsenoberfläche durch die Iris erklärt werden.

Linse Punkte sprechen unserer Meinung nach für den zuletzt genannten Entstehungsmodus.

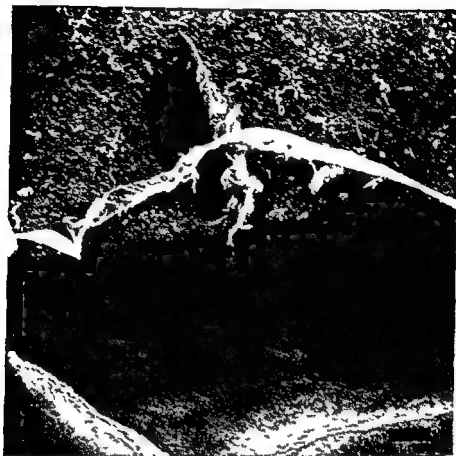
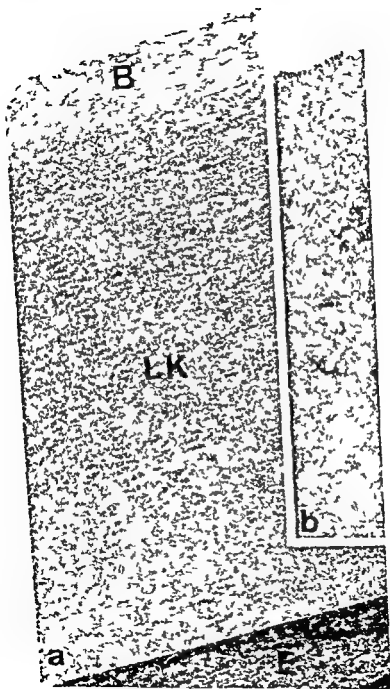


Abb 5

Die der zentralen Scheibe entsprechende oberflächliche Lamelle ist an umschriebener Stelle abgelöst. Sie liegt zum Teil als zusammengerolltes Häutchen in Bildmitte. Paster elektronenmikroskopische Aufnahme C/Au bedampft. Originalvergrößerung 2100 \times .

logisch veränderte Oberflächenstruktur. Einzelne Materialteilchen, die offenbar durch das Kammerwasser verschleppt werden können, der eigentlichen Scheibe aufgelagert sein. Auf der niveaumässig tiefer gelegenen intermediären Zone finden sich unregelmässig verstreute polymorphe Teilchen.

Unsere klinischen und ultrastrukturellen Untersuchungen lassen es sehr wahrscheinlich erscheinen, dass die zentrale Scheibe durch das Pupillenspiel geformt wird, wobei in der intermediären Zone ein grosser Teil des Exfoliationsmaterial abgerieben wird. Die spaltlampenmikroskopisch sichtbaren granulären Veränderungen entstehen offenbar unter einer bestimmten mechanischen Belastung. Sie können nicht nur peripher, sondern auch zentral auftreten, wie dies eine entsprechende Beobachtung Horvén's (1935) zeigte (Scheuern von Pupillarmembranfasern auf der zentralen Scheibe).



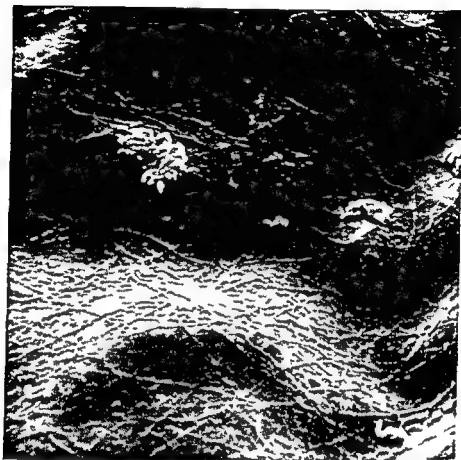


Abb 7

Oberflächenstruktur einer normalen vorderen Linsenkapsel Rasterelektronenmikroskopische Aufnahme C/Au bedampft Originalvergrößerung 10 500 ×

a) Die von uns beobachtete langsame Entwicklung des Vollbildes einer so genannten Kapselabschilferung aus einer gleichförmigen die ganze einsehbare Linsenvorderfläche einnehmenden Veränderung. Wurde es sich um einen Niederschlag bestimmter Substanzen aus dem Kammerwasser handeln, wäre eher zu erwarten, dass die intermediäre Zone von allen Anfang an frei von aufgelagertem Material bliebe, da dieses durch das Pupillenspiel ständig abgerieben werden musste.

Abb 8a-8b

8a Zentrale Zone der vorderen Linsenkapsel Homogen strukturierte ca 23 µ dicke Linsenkapsel (LK) übergehend in ein ca 15 µ breites fibrilläres Band (B) Linsenepithel (E) Transmissionselektronenmikroskopische Aufnahme Vergr. 4 200 ×
8b Intermediärzone Homogen aufgebaute Linsenkapsel ohne fibrilläre Oberflächenschicht Transmissionselektronenmikroskopische Aufnahme Vergr. 1: 400 ×



Abb. 10

Interelektrolytische Struktur bestehend aus groben (Durchmesser ≈ 100 nm) und feinen Fibrillen. Transmissionselektronenmikroskopische Aufnahme. Vergr. $\times 500$.

Während Sunde und Bertelsen annahmen, dass das Material der zentralen Scheibe sehr leicht bei der Reparation verloren gehen könnte, hatten wir keine Schwierigkeiten dieses zu erhalten. Nach unserer Meinung haftet die zentrale Lamelle zumindest so fest auf der Unterlage wie das Material der granularen Zone. So konnten wir an allen Linsen die Veränderungen, die wir an der Spaltlampe



Abb 9

Zentrale Zone der vorderen Linsenkapsel bei stürkerer Vergrößerung. Das fibrillare Band ist durch dicke Fibrillen (↓) mit einem mittleren Durchmesser von 330 Å und periodischen Substanzverdichtungen charakterisiert. Transmissionselektronenmikroskopische Aufnahme. Vergr. 23 660 ×.

b) Der umgekehrte Vorgang, dass sich nämlich bei einer voll ausgeprägten Kapselabschilferung brückenartige Verbindungen zwischen der Scheibe und der granularen Zone in einer vorher klaren intermediären Zone ausbilden konnte, weder von anderen Autoren noch von uns beobachtet werden. Akzeptiert man die Niederschlagstheorie, wäre diese klinische Tatsache zwanglos nur unter der Annahme erklärbar, dass das später abgelagerte Material nicht ständig, sondern nur in einer bestimmten Phase des pathologischen Prozesses gebildet wird.

c) Entfernt man die zentral gelegene degenerierte Lamelle, erscheint nicht die glatte Oberfläche einer normalen Linse, sondern eine deutlich veränderte Linsenkapsel (Abb 7).

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Anschr d Verf

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gesehen und graphisch festgehalten hatten in allen Einzelheiten bei der Betrachtung am Rasterelektronenmikroskop wieder erkennen

Bis jetzt liegen unserer Meinung nach keine einwandfreien Beweise vor wie und aus welchem Gewebe die Fibrillen des Exfoliationsmaterials entstehen. Eine Fibrillogenese setzt die unmittelbare Nachbarschaft einer Zelle nicht unbedingt voraus. Es erscheint uns daher vorstellbar, dass es durch eine Störung des normalen Enzymmusters des Kammerwassers zu einer Degeneration bestimmter Strukturen des vorderen Augenabschnittes kommt. Die dafür in Betracht zu ziehende perikapsuläre Membran und die Zonula entstehen nach Schwalbe (1887) und Pau (1907) auf dem Boden der Tunica vasculosa lentis. Damit fand die vorgestellte Theorie auch von embryologischer Seite eine Stütze, da gerade diese Gewebsabschnitte beim Exfoliationssyndrom die ausgeprägtesten Veränderungen zeigen. Ehe jedoch die pathogenetischen Zusammenhänge nicht mit letzter Sicherheit geklärt sind, erscheint es uns durchaus zweckmässig, die ursprüngliche Krankheitsbezeichnung Vogts "Kapselhautcher Abschlüpfung" oder besser noch den von Sunde geprägten Terminus "Exfoliationssyndrom" beizubehalten und mit dem Zusatz "sogenannte (s)" allen noch bestehenden Zweifel Rechnung zu tragen.

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where V is the visual acuity (the reciprocal of resolution expressed in minutes of arc) d is the diameter of the aperture and c is a constant

It is well known that this equation is valid for the resolution of two point sources of light. The first part of this communication (Hallden 1943) discussed the value of the constant c . With sodium light (wave length 0.00059) the classical Rayleigh criterion of resolution gives $c = 0.404$. A limit of no resolution was calculated and was found to be $c < 0.53$ and consequently $0.404 < c < 0.53$.

For the human eye the Stiles Crawford effect might possibly reduce the effect of diffraction and improve the resolving power of the eye but calculation showed that this improvement is very slight.

It is less generally known that the same equation applies to a periodic test object like a grating. Abbe (1873) showed that diffraction by the test object then becomes the important process in place of diffraction by the aperture of the optical system. Abbe's experiments and calculations were for the case of the microscope. Porter (1906) showed that the results are valid for macroscopic optics but it is not certain that they can be immediately applied to the visual resolution as has been done by Hartridge (1918-19) who found a value of c about as large as that for the resolution of two point sources of light.

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The diffraction patterns of most ordinary test objects are exceedingly complicated and it would be difficult to find the limits of resolution by calculation. An easier method seems to be the empirical one. Equation (1) is determined by

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DIFFRACTION AND VISUAL RESOLUTION

II The resolution of Landolt's ring

BY

ULF HALLDÉN

It is known that when diffraction is the limiting factor of resolution the resolution of two point sources of light and that of a grating are inversely proportional to the diameter of the aperture. Here it is shown that the same relation is valid for the visual resolution of the Landolt ring test object. A comparison of the resolution when limited by diffraction of the Landolt ring and of two point sources of light shows that the resolution of the former is much better. This explains the clinical observation that patients treated with miotics often have better visual acuity than would be expected from the diameters of their pupils.

The visual resolution of two point sources of light is limited by diffraction when the diameter of the pupil is less than 2.5 mm; the corresponding value for the resolution of the Landolt ring is about 1 mm.

Key words: diffraction - grating - Landolt's ring - resolution - useful magnification - visual acuity

When diffraction is the limiting factor of visual resolution the resolution varies directly with the wave length of light and inversely with the diameter of the aperture. If the wave length is fixed the relation can be expressed by the equation

$$V = c \cdot d \quad (1)$$

where V is the visual acuity (the reciprocal of resolution expressed in minutes of arc) d is the diameter of the aperture and c is a constant

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The diffraction patterns of most ordinary test objects are exceedingly complicated and it would be difficult to find the limits of resolution by calculation. An easier method seems to be the empirical one. Equation (1) is determined by

diffraction and it seems reasonable to expect that the same constant c for any test object. The numerical value of the constant c is the wave length of light but it seems probable that for a given test object c is determined by the test object. It might be possible to verify experimentally and find the value of the constant c by using test objects that does not differ too much from the usual visual acuity charts.

Material and Methods

For apertures of different diameters was met by a series of experiments. The possibility of using miotics and measuring the entrance pupil for several practical reasons it is less comfortable for the observer. Miotics might disturb the results and it might be difficult to measure small diameters. Miotics were discarded on theoretical grounds as the theory of diffraction with a circular aperture is exactly valid only when the aperture is in front of or coincides with the first refracting surface. For artificial pupils stenopeic holes from a trial case were used. The holes were made from aluminum foil which was blackened and perforated with needles. A great number of such holes were made and examined. Many were irregular and had to be discarded and only a few could be used. These were examined and measured using a Haag Streit corneal reflexometer the old model which can easily be arranged for projection so that the image of the artificial pupil magnified about 100 times is projected on a screen. In this way the error of measurement of the artificial pupil was about 0.02 mm.

For illumination of the test object I used sodium light which for the purpose of the investigation can be regarded as monochromatic with a wave length of 589 mm. In all experiments the distance from the 35 W sodium lamp to the test object was proportional to the diameter of the artificial pupil so that the retinal illumination was kept approximately the same for all artificial pupils at about 300 troland.

Thought was given to the choice of test object. Ordinary visual acuity charts could not be used because the legibility of the test letters varies significantly (Snellen 1964). For a preliminary series of experiments the Snellen chart was used but it was felt that the Landolt ring was more practical. A series of cards were produced photographically and each card had six Landolt rings. Each ring opened in one of four directions. The measurements of visual acuity were performed by forced guesses. The probability of guessing

correctly the position of the gap of one unresolved ring is $1/4$ and of guessing all six rings of one card $1/4096$. The gaps in the rings were 1.03 mm and the visual angle was changed by changing the distance of observation. In a typical measurement the first observation was made at a distance where the gaps were unresolved, the distance was reduced by 0.5 m increments (or below 3 m by 0.25 m) and the observation repeated on another card and so on until all six rings of one card were read correctly. If a number of such observations are necessary for each measurement the chance of a lucky guess is of course increased. After some training however it was possible to judge the starting distance so well that the number of observations of each measurement was reduced to 2-4 and the probability of a successful guess was about $1/1000$. A disadvantage of using Landolt rings with more than two positions of the gap is that astigmatism might influence the result but no measurable astigmatism occurred among the subjects. The small artificial pupils will reduce the importance of astigmatism and also of spherical aberration. All subjects have normal visual acuity and wore spherical correcting glasses during the experiments. Measurements were performed with five eyes of four subjects.

The work with small artificial pupils meets with one difficulty which merits discussion. They act as stereopic holes and thus visualize entoptical phenomena originating in the media of the eye (Helmholtz 1969, vol. I pp. 204-212). The illumination was not arranged in the same way as in the experiments described by Helmholtz and the media of the subjects were clinically clear but even with the smaller pupils some irregularities were visible. The reading of the cards was slower with the smallest artificial pupils because of those irregularities and it is difficult to prove that the resolution was not somewhat impaired. This source of error might result in values of the visual acuity which would be too low.

Results

The regression of visual acuity on diameter of aperture

The results are presented as diagrams Figs. 1-5. The diameters of the artificial pupils are given on the horizontal axes, the visual acuities on the vertical ones.

The measurement of the visual acuity is always rather inexact even if it is carefully performed. Each of the values of visual acuity given in the diagrams is the mean of 5-7 measurements. The means are calculated according to the method presented in an earlier communication (Hälldén 1972, eq. 4). The correction for midvalues of class intervals was not used for two reasons: firstly

the nature of diffraction and it seems reasonable to expect that the same equation is valid for any test object. The numerical value of the constant c is influenced by the wave length of light but it seems probable that for a given wave length c is determined by the test object. It might be possible to verify this hypothesis experimentally and find the value of the constant c by using a test object which does not differ too much from the usual visual acuity charts.

Material and Methods

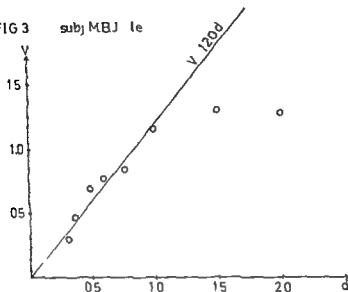
The need for circular apertures of different diameters was met by a series of artificial pupils. The possibility of using miotics and measuring the entrance pupil was rejected for several practical reasons: it is less comfortable for the subjects, accommodation might disturb the results, and it might be difficult to achieve very small diameters. Miotics were discarded on theoretical grounds as well as the theory of diffraction with a circular aperture is exactly valid only if the aperture is in front of or coincides with the first refracting surface. For the larger artificial pupils stenopeic holes from a trial case were used. The smaller ones were made from aluminum foil which was blackened and perforated with needles. A great number of such holes were made and examined; most of them were irregular and had to be discarded, and only a few could be used. The holes were examined and measured using a Haag Streit corneal microscope of the old model which can easily be arranged for projection so that a real image of the artificial pupil magnified about 100 times is projected onto a screen. In this way the error of measurement of the artificial pupils was about 0.02 mm.

For the illumination of the test object I used sodium light which for the purpose of the investigation can be regarded as monochromatic with a wave length of 0.00059 mm. In all experiments the distance from the 95 W sodium lamp to the test object was proportional to the diameter of the artificial pupil. In this way the retinal illumination was kept approximately the same for all artificial pupils at about 300 troland.

Some thought was given to the choice of test object. Ordinary visual acuity charts could not be used because the legibility of the test letters varies significantly (Dreyer 1964). For a preliminary series of experiments the Snellen illiterate E was used but it was felt that the Landolt ring was more practical. A number of cards were produced photographically and each card had six Landolt rings. Each ring opened in one of four directions. The measurements of visual acuity were performed by forced guesses. The probability of guessing

FIG 3

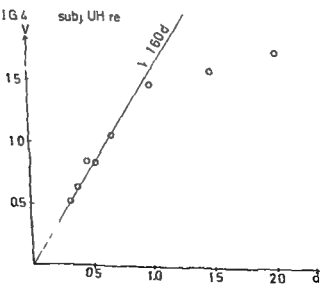
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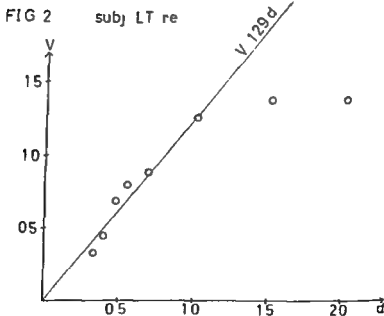
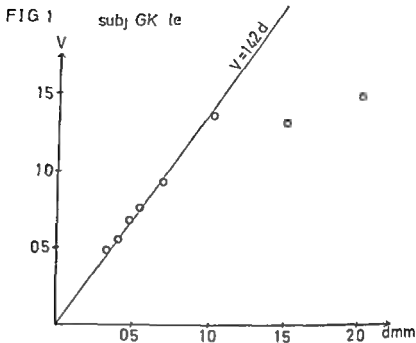


because the steps of measurements were small and therefore the correction unimportant and secondly because it is valuable for the discussion to be quite certain that the values of the visual acuity are not too high

FIG 4

sub_j UH re





Figs 1-2

The abscissae give the diameter of the artificial pupil the ordinates the visual acuity. Each circle represents the mean of 5-7 measurements of the visual acuity. The fine lines are the lines of regression as calculated.

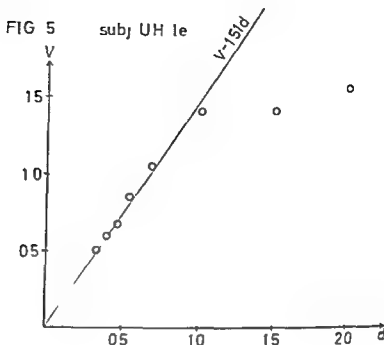
Table 1

Subject	Mean value of c	Standard deviation	Number of measurements	Standard error of mean
GA	1.42	0.14	38	0.07
LT	1.09	0.29	31	0.04
MBJ	1.00	0.20	23	0.04
UH re	1.60	0.21	30	0.04
UH le	1.51	0.15	30	0.03

It is useful to discuss the possibility of error. The random errors of the mean values are small as is shown statistically. The errors of measurement of d are very small. The measurements of V were performed according to clinical usage: all six rings should be read correctly and corrections for mid values of class intervals were not used. This as well as the entoptical phenomena might give values of V which are a little too low. When c was calculated the values with $d = 1$ mm were included. It is possible however that the limit of linear regression is somewhat below 1 mm. This would give values of c which are slightly too low.

Discussion

The calculated value of c for the resolution of two point sources of light is $0.404 < c < 0.53$. The empirical value of c for the resolution of Landolt's ring is two to four times larger: allowing for individual variations it ranges between 1.2 and 1.6. This result gives an adequate explanation of the clinical observation which initiated this study: namely the well known fact that many patients treated with miotics have a good visual acuity much better than could be expected from the diameter of their entrance pupils. The charts for the clinical measurement of the visual acuity are constructed on the same principle as Landolt's rings but differ much from the two point sources of light and from the grating. The concept of the double star introduced by Hooke has been fruitful in the discussion of the density of retinal cones but it is not equally applicable to the problem of the influence of diffraction on the clinical visual acuity.



It is immediately seen from the diagrams that if the artificial pupil is small the visual acuity is directly proportional to the diameter of the pupil. With a larger pupil the visual acuity is relatively lower, as might be expected if factors other than diffraction are influencing the visual resolution. The limiting value is 1 mm or somewhat less; below this value the regression seems to be linear.

The value of the constant of proportionality

The constant of proportionality is $c = V/d$ when d is so small that V is limited by diffraction. It is possible to determine c by a single measurement of the visual acuity with an artificial pupil so small that the investigator is certain that the resolution is limited by diffraction. Here we will use all values with $d = 1$ mm or less. The results are collected in Table I.

It is remarkable that there are individual differences. Those cannot be explained by the optics of diffraction. They might be caused by different training in the interpretation of the diffraction patterns of the test object (subject UH has been experimenting with Landolt's rings for many years) or they might be connected with the entoptical phenomena mentioned above.

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FREQUENCY OF CAPSULAR GLAUCOMA IN CENTRAL FINLAND

BY

ULF KRAUSE

In a hospital series of 277 consecutive glaucoma cases in Central Finland senile open angle glaucoma was observed in 137 patients (61.7%). Simple glaucoma was present in 79 (35.6%) of these, capsular glaucoma in 59 (76.1%). The simple glaucomas constituted 57.7% and the capsular glaucomas 47.3% of the senile open angle glaucomas. The proportion of capsular glaucoma clearly grew with increasing age and constituted 61.5% in the oldest age group (80-89 years). Capsular glaucoma was diagnosed at a mean age of 67.9 years, simple glaucoma 7.3 years earlier. Despite the fact that pseudoexfoliation of the lens is more frequent in Finland than in Norway the capsular glaucomas constitute about 40% of the hospitalized senile open angle glaucomas in both countries.

Key words: capsular glaucoma - simple glaucoma - frequency - Finland
exfoliation - fibrillographia epitheliocapsularis

There is a wide range of variation in the frequency of open angle glaucoma with pseudoexfoliation of the lens capsule (capsular glaucoma) reported in hospital series. The lowest frequency (4%) was observed by Irvine (1940) and Lemoine (1950), the highest (93%) by Horven (1936). Strikingly high values have been indicated in several Norwegian reports (Table I) but investigators in other countries have also noted a high frequency of capsular glaucoma.

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The observation that the limitation of resolution by diffraction is influenced by the test object might be of interest in the theory of optical instruments. The concept of useful magnification means the minimum value required to realize the full resolving power of an instrument: the limit of the resolving power is in principle set by diffraction. As this limit is not equal for all test objects the useful magnification might be different for different purposes. The ability to resolve two point sources of light might be more important for an astronomical telescope than for an instrument intended for terrestrial use.

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FREQUENCY OF CAPSULAR GLAUCOMA IN CENTRAL FINLAND

BY

ULF KRAUSE

In a hospital series of 972 consecutive glaucoma cases in Central Finland senile open angle glaucoma was observed in 137 patients (61.7%). Simple glaucoma was present in 79 (35.6%) of these capsular glaucoma in 53 (76.1%). The simple glaucomas constituted 57.7% and the capsular glaucomas 42.3% of the senile open angle glaucomas. The proportion of capsular glaucoma clearly grew with increasing age and constituted 61.5% in the oldest age group (80-89 years). Capsular glaucoma was diagnosed at a mean age of 67.9 years, simple glaucoma 73 years earlier. Despite the fact that pseudoexfoliation of the lens is more frequent in Finland than in Norway, the capsular glaucomas constitute about 40% of the hospitalized senile open angle glaucomas in both countries.

Key words: capsular glaucoma - simple glaucoma - frequency - Finland
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Table I

The frequency of capsular glaucoma among hospital patients in Norway

Horven E (1936)	93 %
Holst (1941)	82 %
Thomassen (1949)	79 %
Petersen (1958)	77 %
Aasved (1971b)	~ 40 %

among hospital patients (e.g. Joannides Katsourakis & Velissaropoulos 1961 89.5 % Baumgart 1933 49 %) The Norwegian investigations are the only ones performed in Scandinavia The occurrence of pseudoexfoliation of the lens was studied in elderly people in central Finland (Krause Helve & Forsius 1973) A rise in frequency from 10 % in the age group 60–69 years to 33.8 % in the group 80–89 years was observed In Norway the frequency figures obtained in the corresponding age groups were 1 % and 7.9 % (Aasved 1971a) Considering the high frequency of pseudoexfoliation of the lens capsule in Finland the percentage of hospital patients with capsular glaucoma was presumed to be particularly high in Finland higher for instance than the 40 % reported in Norway (Aasved 1971b) The purpose of the present investigation was to analyse the distribution of simple and capsular glaucoma in a Finnish hospital series

Material and Methods

The series consisted of 222 patients 85 male and 137 female admitted to the Oulu University Eye Hospital in 1971 with a diagnosis of glaucoma Of the different types of glaucoma only simple and capsular glaucoma were investigated The criteria for a diagnosis of simple glaucoma were a repeated elevation of the intraocular pressure to at least 22 mmHg the presence of papillary excavation and/or defects of the visual field a rise in pressure on provocative tests an open chamber angle as revealed by gonioscopy and absence of signs indicating any obvious disease of the eye A diagnosis of capsular glaucoma presupposed in addition that definite signs of exfoliation at the pupillary margin lens or corneal endothelium were seen on mydriasis

The patients' ages and the age when glaucoma was diagnosed were recorded Patients with chronic simple glaucoma in one eye and capsular glaucoma in the other were omitted from the analysis

If a patient had been admitted more than once during the year in question only the chronologically first admission was taken into account The numbers given in what follows denote patients not eyes

Results

During 1971 292 patients (85 male and 197 female) with various types of glaucoma were admitted to our hospital (Table II). Of these 79 (35.6%) had simple glaucoma and 58 (26.1%) capsular glaucoma. These two groups constituted 61.7% of the total number of glaucoma patients. Eighty-five patients (38.3%) had some other type of glaucoma. Of the 79 patients with simple glaucoma 24 were male and 55 female. The mean age in this group at the time of hospitalization was 64.8 years; the mean age of the males was 62.4 years; the mean age of the females 65.8 years. The mean age when simple glaucoma was diagnosed was 60.6 years. Capsular glaucoma was present in 58 patients: 26 male and 32 female. The disease was bilateral in 41 cases and unilateral in 17. The mean age in this group was 70.9 years; the mean age of the males was 70.7 years; the mean age of the females 71.0 years. The mean age when glaucoma was diagnosed was 67.9 years.

The greatest number of simple glaucomas were found in the age group 60-69 years, but the capsular glaucomas increased in frequency up to an age of 70-79 years (Fig. 1). The patients with simple glaucoma constituted 81.8% of the age group 40-49 years and 90% of the age group 50-59 years. After this the frequency of simple glaucoma decreased so that these patients constituted 58.1% of the age group 60-69 years, 44% of the group 70-79 years and 38.5% of the group 80-89 years. The corresponding figures for capsular glaucoma were 18.2%, 10.0%, 41.8%, 56% and 61.5% (Fig. 2).

Table II
Sex distribution of glaucoma cases

Diagnosis	No. of cases		Total
	Male	Female	
Simple glaucoma	24	55	79
Capsular glaucoma	26	32	58
Secondary glaucoma	15	18	33
Closed angle glaucoma	12	21	33
Pigmentary glaucoma	—	4	4
Simple glaucoma with contralateral capsular glaucoma	5	5	8
Juvenile glaucoma	3	2	5
Syndrome Posner-Schlossman	1	—	1
Mixed glaucoma	1	—	1
Total	85	197	282

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among hospital patients (e.g. Joannides Katsourakis & Velissaropoulos 1961 39.5 %, Baumgart 1933 49 %). The Norwegian investigations are the only ones performed in Scandinavia. The occurrence of pseudoexfoliation of the lens was studied in elderly people in central Finland (Krause Helve & Forsius 1973). A rise in frequency from 10 % in the age group 60-69 years to 37.8 % in the group 80-89 years was observed. In Norway the frequency figures obtained in the corresponding age groups were 1 % and 7.9 % (Aasved 1971a). Considering the high frequency of pseudoexfoliation of the lens capsule in Finland the percentage of hospital patients with capsular glaucoma was presumed to be particularly high in Finland higher for instance than the 40 % reported in Norway (Aasved 1971b). The purpose of the present investigation was to analyse the distribution of simple and capsular glaucoma in a Finnish hospital series.

Material and Methods

The series consisted of 222 patients 85 male and 137 female admitted to the Oulu University Eye Hospital in 1971 with a diagnosis of glaucoma. Of the different types of glaucoma only simple and capsular glaucoma were investigated. The criteria for a diagnosis of simple glaucoma were a repeated elevation of the intraocular pressure to at least 22 mmHg, the presence of pupillary excavation and/or defects of the visual field, a rise in pressure on provocative tests, an open chamber angle as revealed by gonioscopy and absence of signs indicating any obvious disease of the eye. A diagnosis of capsular glaucoma presupposed in addition that definite signs of exfoliation at the pupillary margin, lens or corneal endothelium were seen on mydriasis.

The patients' ages and the age when glaucoma was diagnosed were recorded. Patients with chronic simple glaucoma in one eye and capsular glaucoma in the other were omitted from the analysis.

If a patient had been admitted more than once during the year in question only the chronologically first admission was taken into account. The numbers given in what follows denote patients, not eyes.

in the highest age groups constituting 56.0% in the age groups 70-79 years and 61.5% in the group 80-89 years and that capsular glaucoma was diagnosed at a mean age of 67.9 years or 7.3 years later than simple glaucoma.

The indications for hospitalization were similar in all cases and independent of the presence or absence of pseudoexfoliation. It goes without saying that a younger patient with uncompensated simple glaucoma is considered a more urgent case than an old person who has received a maximum of conservative treatment for capsular glaucoma and can in no event be operated upon. This rule applies irrespective of whether the rise in ocular pressure is compensated or not. Hence the figures presented probably do not reflect the real need for treatment; the group of capsular glaucoma should perhaps have been somewhat larger.

Three men and five women had simple glaucoma in one eye and capsular glaucoma in the other. For obvious reasons these patients were omitted from the analysis.

In the region of our hospital the frequency of pseudoexfoliation of the lens among the elderly was found to be 10.0% in the age group 60-69 years, 21.3% in the group 70-79 years and 32.8% in the group 80-89 years (Krause, Helve & Forsius 1953). Of the present 137 patients with senile open angle glaucoma 79 (57.6%) had simple and 58 (42.3%) capsular glaucoma. It is therefore very likely that in many of the present cases of capsular glaucoma pseudoexfoliation of the lens played no part in the development of the increased intraocular pressure.

In a Norwegian hospital series of 277 patients with open angle glaucoma investigated by Aasved (1952a) 110 (about 40%) had capsular glaucoma. The corresponding figure in the present series is 42.3%. Despite the fact that pseudoexfoliation of the lens is much more frequent among the aged in Finland than in Norway the need for hospital treatment unexpectedly appears to be of the same order of magnitude.

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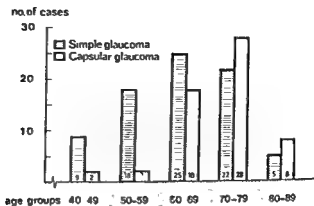


Fig. 1

The number of cases of simple and capsular glaucoma in different age groups (137 cases)

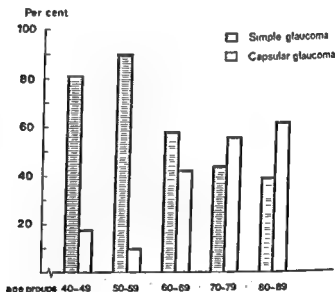


Fig. 2

The distribution of simple and capsular glaucomas among senile open angle glaucomas

Discussion

Of the total series of 222 patients 35.6% had simple glaucoma and 26.1% capsular glaucoma. The higher frequency of simple glaucoma was in part due to the infrequent occurrence of pseudoexfoliation in the younger age groups. The fact that capsular glaucoma is in general a disease of old age was also brought out by the findings that this was the main type of open angle glaucoma

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OPTOCILIARY VEINS DISC PALLOR AND VISUAL LOSS

A triad of signs indicating sphenoidal orbital meningioma

BY

LARS FRISÉN WILLIAM F HOYT and BJÖRN M TENGROTH

Four middle aged women presented with unilateral long standing blindness. All four had a poorly demarcated and atrophic optic disc and prominent optociliary veins. All had meningioma of the cranio orbital junction. It is postulated that the optociliary veins in this setting indicate indolent tumor growing in the distal perioptic meninges.

Key words: optociliary veins ; circulation of the eye - optic nerve - optic atrophy - perioptic meningioma

A triad of optociliary veins, optic atrophy and long standing blindness was recorded in four middle aged women examined in the neurosurgical wards at the University of California Medical Center in San Francisco during a three year period. Three had mild ipsilateral proptosis. All had meningioma involving the cranio orbital junction.

This report documents photographically the appearance of these patients' optociliary veins and atrophic optic discs, presents fluorescein fundus angiograms showing that blood in the central retinal vein is diverted into peripapillary choroidal channels and discusses pathogenesis and specificity of these clinical signs in relation to indolent tumor in the perioptic meninges.

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Case Reports

Case 1

(P B # 259092) A 45 year old housewife who lost the sight in her left eye when a teenager was first examined at the University of California when she was 37 years old. Her left eye was blind with marked pallor of the optic disc and a peculiar cluster of vessels on the disc surface which were interpreted at that time as an "incidental anomaly or hemangioma". Visual acuity fields and the fundus of the right eye were normal. Radiologic studies showed hyperostosis of the left anterior clinoid process but pneumoencephalograms provided no indication of a mass in the prechiasmatic cistern. She was discharged from the hospital and her visual fields were tested yearly intervals for 13 years. During this time function in her right eye remained normal. When she complained of recurrent headaches at 45 years of age she again was admitted to the University Hospital for re-evaluation of her sphenoid tumor.

Ocular findings in the left eye included slight exotropia and proptosis (7 mm) 10 per cent limitation of eye movement in all directions, normal consensual pupillary response, normal resistance to retropulsion of the globe and total blindness. The left optic disc appeared totally atrophic with indistinct margins, loss of peripapillary nerve fiber reflexes, irregular narrowing of arterioles with sheathing and two large opticiliary veins (Fig 1). The right eye was normal functionally and morphologically. Ophthalmodynamometric pressures in the ophthalmic arteries were equal.

Physical and neurological examinations revealed moderate obesity but were otherwise unremarkable. The protein level in the cerebrospinal fluid was normal. Neuro-radiologic studies showed only a mild increase in the left sphenoid hyperostosis but no significant pneumoencephalographic filling defect in the adjacent cistern. Selective left internal carotid angiograms showed tumor stain in the orbital apex and slight straightening of the carotid siphon.

Comment This middle aged woman had clinical and radiologic signs of an anterior clinoid meningioma which had caused blindness in the left eye 25 years earlier. Her left optic disc was white with blurred margins, sheathed vessels and opticiliary veins (known to be present for at least 13 years). There was minimal proptosis. Diagnosis was sphenoid meningioma with involvement of optic nerve.

Case 2

(E C. # 454265) A 49 year old woman first noted failing vision in her left eye at age 40. One year later, after all radiologic studies failed to show the nature of her optic nerve disease, an exploratory craniotomy exposed a meningioma involving the left optic nerve at the intracranial meniscus of the optic canal. The left eye was blind following surgery and remained so. Four years later vision in the right eye began to dim. Again radiologic studies including carotid angiograms and pneumoencephalograms performed in another hospital failed to show tumor but at craniotomy she had a second intracanalicular meningioma which was growing around the right optic nerve. Part of the tumor was removed and her vision remained stable for another four years before it failed again. At this time she was referred to the University of California Hospital.



Fig. 1

Case 1 left eye. The pale poorly demarcated optic disc has attenuated and partly sheathed arteriole. Ectatic optociliary veins drain into choroid at 3 and 9 o'clock. The absence of nerve fiber layer in this blind eye. Notice that the zone where the veins enter the choroid at 3 o'clock appears darker than the surround.

Ocular findings included blindness of the left eye with complete atrophy blurred disc margins narrow sheathed retinal arterioles and several optociliary veins (Fig 2). There was light perception in the right eye and marked pallor of the optic disc. Neither eye showed evidence of ophthalmoplegia or proptosis. Physical and neurological examinations were normal.

A third neurosurgical exploration was performed but the meningioma had surrounded the carotid artery and the right optic nerve and could not be resected. Histologic diagnosis was meningotheelial meningioma.

Comment This middle aged woman exemplifies two different modes of optic nerve involvement with meningioma. The triad of blindness total optic atrophy with blurred margins and optociliary veins on the left indicates optic nerve sheath involvement while the findings on the right are those of simple optic nerve compression.

The left eye had been blind for eight years.



Figs 2 and 3

Fig 2 Case 2 left eye. At least four tortuous bypass optociliary channels occupy this atrophic disc. Note blurred disc margins perarterial sheathing and total loss of nerve fiber reflexes.

Fig 3 Case 3 right eye. Tortuous optociliary veins at inferior pole of the indistinct disc.

Case 3

(H B # 50 98 45) A 40 year old woman was admitted to the University of California Hospital for complaints of headache progressive weakness of her right leg for six months and blindness of the right eye for 21 years

Ocular examination showed total atrophy of the right optic disc with a cluster of optociliary veins (Fig 3) The right fundus contained no visible nerve fibers There was no proptosis The right eye moved normally in all directions The left eye had normal visual acuity Definite desaturation of colors was present in the temporal hemifield The left optic disc had normal color and the surrounding retina was not depleted of nerve fibers

Fluorescein angiograms proved that the optociliary veins in the right eye drained retinal venous blood into the choroid (Fig 4 A B)

Angiographic and pneumoencephalographic signs indicated a large basal mass growing in the midline with distinct hyperostosis of the planum sphenoidale

At craniotomy the tumor extended from the cribriform plate to the anterior clinoids enveloping both carotid arteries and both optic nerves The right carotid was entered during the dissection of the tumor Bleeding was stopped by clipping the supraclinoid segment Postoperatively the patient had massive right sided cerebral infarction and died Permission for necropsy examination was not granted

Microscopic diagnosis from tumor fragments was psammomatous meningioma

Comment This 40 year old woman developed symptoms of a subfrontal mass after 21 years of unilateral blindness The blind eye presented with a blurred and atrophic disc and optociliary veins indicating indolent meningioma of the optic nerve sheaths

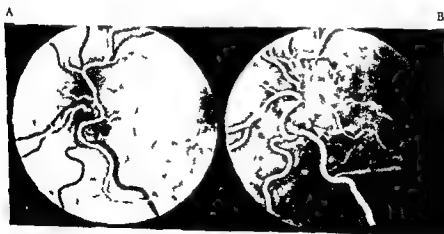


Fig 4

Case 3 Fluorescein angiograms of right fundus

A Optociliary channels are not yet filled in the arterial phase

B Veno phase The optociliary channels are filled from the central retinal vein

Case 4

(R F # 51 63 10) A 55 year old woman who had been committed to a mental institution because of long standing and progressive dementia was transferred to the University of California Hospital for evaluation of right sided proptosis of about 2 years duration. The right eye had been blind for years but the true duration of this symptom could not be determined.

The right eye protruded 5.5 mm relative to the left. Its movements were restricted about 20 per cent in all fields of gaze but there was no ptosis. The pupil reacted normally to consensual light stimulation. The involved eye was totally blind, its optic disc was white with indistinct margins and two optociliary veins bridged from the central retinal vein to the peripapillary choroid. There was no trace of nerve fibers in the peripapillary retina; the arterioles were narrowed and several were sheathed with whitish tissue in the neighborhood of the disc. The left eye was functionally and morphologically normal. There was no sign of a temporal field defect.

Physical and neurologic examinations confirmed that the patient was grossly demented and that she had the signs of a large bifrontal tumor. Her olfactory sense was difficult to assess but she did not seem to be able to perceive odors.

Neuroradiologic studies showed sclerosis of the right greater wing of the sphenoid and the region of the right optic canal. Carotid angiograms confirmed a large subfrontal mass with the dural vascular supply of a meningioma.

At craniotomy there was a large sphenoid meningioma that arose on the right, extended across the midline and invaded the underlying hyperostotic bone and the optic nerve sheaths in the right orbital apex. The anterior extension of the tumor along the optic nerve was not determined but the nerve sheaths and adjacent orbital tissue was involved as far forward as the surgeon could see. The histologic examination of the resected tumor tissue showed typical features of meningioma.

Comment: This middle aged woman had total right sided optic atrophy with indistinct margins and optociliary veins in an eye which had been blind for an indeterminate period. The sphenoid ridge meningioma caused severe frontal lobe dementia several years before proptosis and partial ophthalmoplegia of the right eye was recognized.

Discussion

Optociliary veins were the striking finding in the blind eye in our four cases of sphenoorbital meningioma. Vascular channels of this type diverting retinal blood flow into the choroid are a distinct rarity. Tortuosity and ectasia differentiate these apparently acquired vessels from the equally rare congenital counterpart (Elschnig, 1898; Braune, 1905; Winther, 1939).

Salzmann (1893) and Elschnig (1898), each of whom contributed a histopathologic specimen of optociliary veins with optic nerve sheath meningioma

postulated that constriction of the central retinal vein by the retrobulbar tumor fosters the development of bypass channels within the eye. The gradual obstruction results in a dilation of preformed capillary vessels connecting the central retinal vein and the peripapillary choroid. In the early phase the venous stasis produces disc swelling. Gradually as the optic nerve is strangulated by the tumor disc swelling is replaced by atrophy exposing the venous bypass channels on the flat pale and poorly demarcated optic disc.

Although these events in the evolution of optociliary bypass channels were not documented in our patients the indistinct disc margins and the arteriolar sheathing in the blind eyes lends strong support to our belief that the fundus signs observed here were preceded by a long but unrecognized period of disc swelling. It is probable that the stage of swelling extends over years. We are currently observing a middle aged woman with a two year history of unilateral progressive visual loss and slight proptosis presumably due to perioptic meningioma. Indolent disc swelling has been present since the first examination. The swelling has involuted slowly and tortuous optociliary veins have emerged (Fig. 5).

Rarely optociliary veins may develop from other causes including chronic atrophic papilledema, central retinal vein occlusion and glaucoma. The course and the signs of the underlying disorder allow easy differential diagnosis.

In addition to their long standing orbital involvement all of our patients had signs of sphenoid meningioma although only two have an intracranial mass. One has had radiographically documented sphenoid hyperostosis for more than 13 years and blindness by history for 35 years. We believe that the tumor in all cases originated at the cranio orbital junction from whence it extended both orbitally and intracranially. In a case similar to ours Moore (1965) showed that the perioptic and sphenoid components of the tumor need not be continuous. In his case the mid orbital optic nerve sheaths were microscopically free from tumor. We suggest that the perioptic component derives from a canalicular source by seeding. Orbital extension of meningioma by this route has little tendency to produce proptosis. Minimal proptosis in our patients contrasts sharply to other routes of orbital invasion by meningioma and attests to the indolence of the process.

The triad of long standing blindness, tortuous optociliary veins and a pale poorly demarcated optic disc is also evident in the cases recorded by Elschnig (1945) and Shikano & Shimizu (1963) but its frequency is unknown. In this respect it is interesting that our four cases were recorded in a three year period. We believe that this triad of clinical signs should be regarded as evidence of sphenoidal orbital meningioma especially when encountered in a middle aged woman.

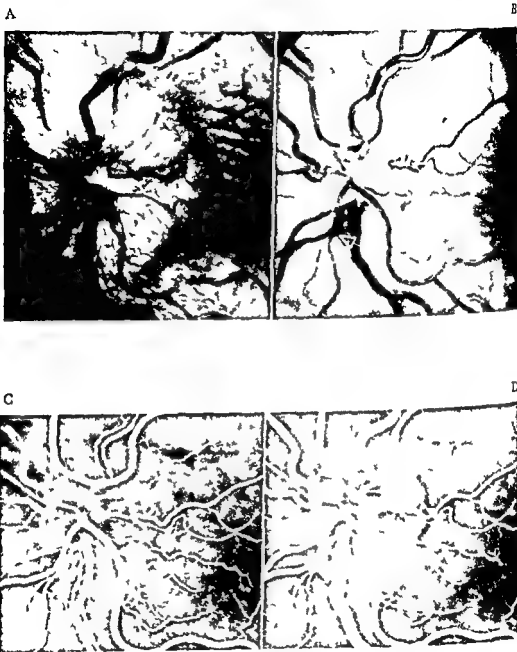


Fig 5

Evolution of optic chiasm shunts

- A Left optic fundus of a 40 year old woman with the clinical signs of peripapillary meningioma. The disc swelling is indolent and associated with choroidal folds. There was a relative paracentral scotoma.
- B Sixteen months later the disc swelling has involuted exposing pallor temporally and multiple optic chiasm shunts (arrows). There was irregular contraction of the peripheral visual field and a marked depression of central function at this time.
- C Arterial phase of fluorescein angiogram corresponding to Fig 5B.
- D Late venous phase shows optic chiasm shunts (arrows).

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ON THE OSCILLATORY POTENTIALS OF THE HUMAN ELECTRORETINOGRAM IN LIGHT AND DARK ADAPTATION

IV Effect of adaptation to short flashes of light Time interval and intensity of conditioning flashes A Fourier analysis

BY

L. WACHTMEISTER

The effect of adaptation to short flashes of light on the oscillatory potentials and the slow potentials (a- and b-wave) of the human ERG as well as the effect on adaptometric visual threshold in response to a series of three flashes were studied. The total energy and the dominant frequency of the oscillatory potentials in response to the third (stimulus) flash were calculated by a combined impulse response and Fourier analysis when the interval between the flashes changed and the intensity of the first two (conditioning) flashes varied.

When recorded in response to flashes given at long intervals or conditioning flashes of low intensity the visual threshold recovered to the scotopic branch of the dark adaptation curve and the oscillatory potentials showed a low energy and high frequency (around 150 Hz). On adaptation to flashes at shorter intervals and more intense conditioning flashes [above the threshold for the appearance of the photopic b-wave in response to the second (conditioning) flash] resulting in the recovery of the visual threshold to the photopic branch of the dark adaptation curve there was an increment of energy and the frequency changed to 105–110 Hz.

The slow potentials (a- and b-wave) and the oscillations were differently affected by adaptation to light by previous flashes. The oscillatory potentials showed a 10-fold gain in energy whereas the amplitudes of the slow potentials were slightly reduced (about 10%).

The oscillatory potentials were optimally recorded in the mesopic range.

of dark adaptation curve – at the limit between the photopic and scotopic visual sensory threshold of retinal sensitivity. Thus one may conclude that the oscillatory potentials seem to reflect photopic activity as well as scotopic processes – probably an interaction between rod and cone activity.

Key words: electroretinography – oscillatory potentials – light and dark adaptation – Fourier analysis – time interval – conditioning light in tenancy – high intensity flashes

The human electroretinogram (ERG) is under certain conditions of stimulation a summation of both rod and cone components which has been postulated by Motokawa & Mita 1942, Adrian 1945, Granit 1947, Johnson 1958, Jacobson 1961, Jayle, Boyer & Saracco 1965 and many others.

In previously dark adapted normal human eye the ERG evoked by the first stimulus (of a pair of stimuli of high luminance) is followed by a period during which the second ERG can be related only to photopic retinal mechanisms (Flenius 1964). Regression lines calculated for the process of recovery of rod function from suppression indicate an exponential recovery both for the a and b wave as well as for the total amplitude of the ERG response. The process of recovery of the a wave starts and is completed earlier than that of the b wave (Elenius 1969). According to Auerbach (1964) an increase of the intervals between the stimuli beyond 15 seconds still results in a small effect on the ERG, but a further increase beyond 25 seconds does not display any detectable change in the pattern of the ERG.

The recovery of the b wave of the corneal ERG after off in a mammalian pure cone retina (squirrel) has also an exponential course which has been suggested to be due to a decay of the suppression process (Tansley, Copenhaver & Cunkel 1961).

There is a much greater and faster reduction of the amplitude of b wave than of the amplitude of the receptor potential recorded intraretinally on Macaca iris (monkey) to a series of stimuli serving both to evoke the electrical potentials and to light adapt the retina (Brown & Watanabe 1965).

Little is known about the behaviour of the oscillatory potentials in this respect.

The oscillatory potentials adapt independently of the slow potentials (a and b wave) to a continuous exposure to background light and the course of recovery in the dark is separate (Algerve & Wachtmeister 1972). The change of sensitivity and relation to stimuli on adaptation to background illumination

seem to some extent reflect the interaction between rod and cone activity (Wachtmeister 1972)

The primary purpose of the present investigation was to study the light adapting effect by previous conditioning flashes on the oscillatory potentials varying the interval and the intensity of the conditioning flashes. A mathematical estimation of the height and frequency of the oscillatory potentials was performed with the aid of a combined impulse response and Fourier analysis

Apparatus and Methods

The manner of recording the ERG was the same as described in the preceding paper (Algere & Wachtmeister 1972). An electronic flash (the light stimulus) delivered a maximum luminance of about 5×10^4 photopic cd/m². Its colour temperature corresponded to about 6500°K. The maximum luminance was reached within 2 msec and then the luminance flux declined exponentially.

The same electronic equipment, calibration and bandpass of the recording system was used as described elsewhere (Algere & Wachtmeister 1972). A Lawwill-Burian contact lens, at which the reference electrode is a part of the contact lens, was used (Lawwill-Burian 1966). The ground electrode was attached to the ear lobe. The electric signal was displayed on a double beam cathode ray oscilloscope (Solartron C\ 1442 B or Hewlett-Packard 132 A) and photographed.

The visual threshold was studied in a Goldmann-Weekers adaptometer. The test target had a visual angle of 10°, maximal illumination of 6 lux and rotatable black parallel stripes.

Methods of measurements

The methods of measurements of amplitudes and peak latencies as well as the mathematical calculation of dominant frequency and energy of the oscillatory potentials were described in detail previously (Algere & Westbeck 1972).

In some of the recordings of the oscillatory potentials to be presented in this study ($5.3 \log I_e = -2$ to -5) (Figs 1a-6a) a Fourier analysis was performed after movement of the origin about 18 msec along the x-axis. The results obtained were nevertheless the same whether or not the first oscillatory peak was included, since the first oscillatory peak during these conditions had a frequency considerably lower (about 60 Hz) than that of the dominating frequency of the oscillatory response. The procedure facilitates the mathematical

evaluation without introducing any error in the interpretation of the results obtained

The adaptometric curve was obtained by noting the visual threshold and time required for the subject to tell if the black parallel stripes had a vertical or horizontal position

The method used gives the visual threshold slightly above that of the perception of light

Procedures

The experimental findings are based on data from two young and healthy persons (one woman and one man). The visual acuity, visual fields, adaptometric visual sensitivity and colour sense were normal. The ERGs shown in the pictures were all recorded from the left eye of the same subject and evaluated by calliper square measurements as well as by Fourier analysis.

The subjects were dark adapted for at least 30 minutes, surface anaesthesia established by Novesin® (Wander) and the pupil of the left eye was expanded to more than 6 mm with Mydrinacil® (Alcon lab). The fellow eye was occluded.

The following two procedures were performed:

I The ERG was recorded after at least 30 minutes of dark adaptation. A series of three flashes of constant and maximal intensity ($\log I = 0$) were given and the ERG in response to the third (stimulus) flash was studied. The first two flashes induced a certain state of adaptation to light and will be referred to as conditioning flashes. The interval between the flashes in each series was successively shortened during the experiment from 5 minutes to 15 seconds.

The visual threshold was determined with the adaptometer after at least 30 minutes of dark adaptation. The light adapting effect of the flashes given as described in the previous paragraph was noted.

II The dependence of the oscillatory potentials on light intensity of the previous (conditioning) flashes was studied. The ERG was recorded in response to the third (stimulus) flash which was of maximal and constant intensity ($\log I = 0$). There was an interval of 30 seconds between each of the flashes in the series of three. Five minutes elapsed between each series to let the retina recover from the light adapting effect by previous stimulation. The intensity of the conditioning flashes was varied over a range of 5 log units ($\log I = -5$ to 0).

The light adaptation induced by the conditioning flashes given as described in the above paragraph was studied by recording the visual threshold with the adaptometer.

seem to some extent reflect the interaction between rod and cone activity (Wachtmeister 1972)

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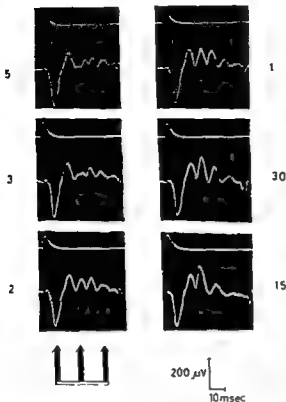


Fig 1 a

Oscillatory potentials of ERG recorded in dark adaptation in response to a series of three flashes of constant and maximal intensity ($\log I = 0$) and varying intervals between flashes. The ERG in response to the third flash in a series of three is shown in each picture. Stimulation pattern is symbolized by vertical arrows (flashes). Black symbol denotes a constant condition, white symbol a variable. Most prominent oscillatory potentials were recorded at intervals of 1 minute or 30 seconds.

(15 seconds) the amplitude was depressed to about $380 \mu V$, making up about 90% of its value in dark adaptation ($400 \mu V$).

The b-wave

The amplitude of the b-wave showed a very slight reduction as the interval decreased down to an interval of 1 minute (Figs 1 b and 2). At shorter intervals

Results

1 TIME INTERVAL

The ERG and the adaptometric visual threshold was recorded after dark adaptation of at least 30 minutes. The intensity of the stimulus light was of constant and maximal intensity ($\log I_s = 0$). The interval varied between 5 minutes and 15 seconds.

The oscillatory potentials

The appearance of the oscillatory potentials changed as the interval between the flashes decreased (Fig. 1a). The first oscillatory peak, ample and dominating, was followed by a marked negativity which in turn was succeeded by small and discrete oscillations when the interval between the flashes was long (up to 3 minutes). The oscillatory potentials were similar to those recorded in dark adaptation prior to any adaptation by light stimulation (*cf* Alleva 1968). As the interval was successively shortened the oscillatory peaks increased and reached a maximum at an interval of 30 seconds. At an interval of 15 seconds only the first three oscillatory peaks were recordable.

The energy of the oscillatory potentials was low when recorded at long intervals (Fig. 2). As the interval got shorter than 3 minutes there was a marked increase in energy which seemed to reach a maximum at an interval of 30 seconds.

The dominant frequency of the oscillatory potentials showed an even decrease from around 150 Hz to around 105 Hz as the interval diminished from 5 minutes to 15 seconds (Fig. 3).

The peak latency of the first and third oscillatory peak (O_1 and O_3) did not show any significant change (Fig. 4). As the interval between the flashes decreased the latency of the second oscillatory peak (O_2) decreased about 5 msec. The latency of the fourth oscillatory peak (O_4) seemed to increase at shorter intervals and the fourth oscillatory peak was not recordable with the shortest interval used (15 seconds).

The interval between the first and the last oscillatory peak (O_1-O_4) increased about 3 msec as the interval diminished which was also demonstrated as a decline in frequency (Fig. 3).

The a wave

The amplitude of the a wave showed an even and slight decrease as the stimulation interval was shortened (Figs. 1b and 2). At the shortest interval

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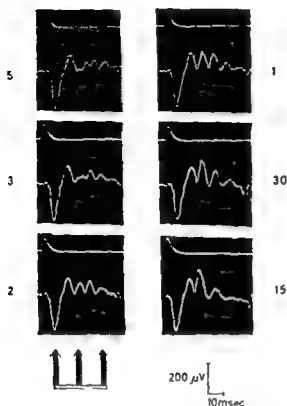


Fig 1a

Oscillatory potentials of ERG recorded in dark adaptation in response to a series of three flashes of constant and maximal intensity ($\log I = 0$) and varying intervals between flashes. The ERG in response to the third flash in a series of three is shown in each picture. Stimulation pattern is symbolized by vertical arrows (flashes). Black symbol denotes a constant condition, white symbol a variable. Most prominent oscillatory potentials were recorded at intervals of 1 minute or 30 seconds.

(15 seconds) the amplitude was depressed to about $350 \mu V$ making up about 90% of its value in dark adaptation ($400 \mu V$).

The b-wave

The amplitude of the b wave showed a very slight reduction as the interval decreased down to an interval of 1 minute (Figs 1b and 2). At shorter intervals

there was a more distinct depression of the b wave. At the shortest interval its amplitude was about $220 \mu V$ making up about 80% of its value in dark adaptation ($270 \mu V$)

It appears from this experiment that the oscillatory potentials behaved entirely different to the slow potentials. The energy of the oscillatory potentials was measured to be larger whereas the slow potentials were smaller than in dark adaptation the closer the flashes were delivered. There was only a slight reduction of the slow potentials (about 10–20%) The oscillatory potentials on the other hand gained markedly in energy (about 10 times) as the interval between the flashes shortened.

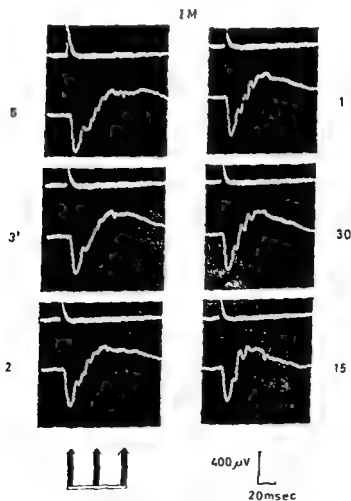


Fig 1b

Amplitudes of the a and b wave of ERG recorded in dark adaptation as described in Fig 1a. Stimulation pattern as in Fig 1a

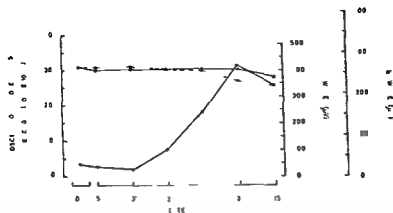


Fig 4

Calculated energy of the oscillatory potentials shown in Fig 1 a and amplitudes of the a and b wave shown in Fig 1 b in relation to interval between stimulus flashes of maximal intensity ($\log I_0 = 0$). There was a gain in energy of the oscillatory potentials when shorter intervals than 3 were used.

Adaptometric visual threshold

During undisturbed dark adaptation after preadaptation to about 8×10^3 photopic cd/m² for 5 minutes the rod cone break of the adaptometric curve (Kohlrausch kink) occurred at a sensory threshold of about $\log R \times 10^3$ lux. Stimulus flashes of maximal intensity ($\log I_0 = 0$) given at the longest inter-

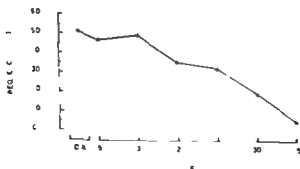


Fig 5

Dominant frequency of the oscillatory potentials of the ERGs shown in Fig 1 a in relation to intervals between stimulus flashes. Stimulus flashes of maximal intensity ($\log I_0 = 0$). There was a decline in frequency from 146 Hz to 105 Hz as the interval between the flashes decreased.

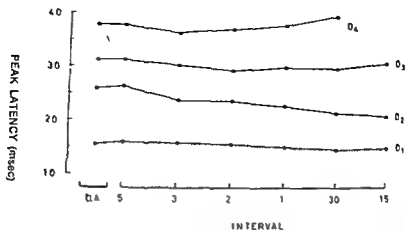


Fig 4

Peak latencies of the individual oscillatory potentials (O_1 , O_2 , O_3 , O_4) plotted against interval between stimulus flashes from ERG's shown in Fig 1 a. The latency of the first, the third and the fourth oscillatory peak (O_1 , O_3 , O_4) showed no distinct change. The latency of the second peak (O_2) decreased when the interval between stimulus flashes decreases. The average error of repetitive calliper square readings was less than 0.5 msec.

val used (5 minutes) rose the sensory threshold of retinal sensitivity very slightly above the absolute threshold (6×10^{-5} lux) (Fig 5). The third (stimulus) flash in each series of three was applied when the visual threshold was still below 6×10^{-5} lux when longer intervals than 30 seconds were used. When the intervals between the flashes were shorter the sensitivity was about 6×10^{-5} lux and the threshold determined by the cone mechanism.

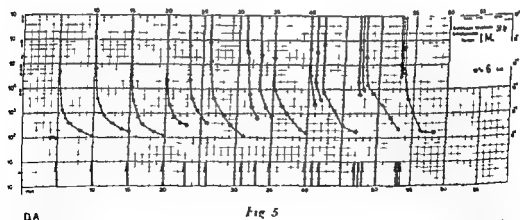


Fig 5

Adaptometric visual threshold in the dark after light adaptation by stimulus flashes elicited at different intervals as in Fig 1. The adaptometric curve was obtained by noting the time required for the subject to distinguish whether the test pattern at various intensities was vertical or horizontal.

1 M

LOG 5.0

LOG 2.0

LOG 4.0

LOG 1.0

LOG 3.0

LOG 0.0



200 μ V
10 msec

Fig 6a

Oscillatory potentials of ERG recorded after conditioning light adaptation from flashes of different intensities. ERGs were recorded in darkness at an interval of 30 seconds. There were 5 minutes between each series of three flashes. The intensity of the first two (conditioning) flashes successively increased and the third (stimulus) flash was of maximal intensity (log = 0). The ERG in response to the second and the third flash in a series of three is shown in each picture. Symbols of stimulation pattern as in Fig 1. Most prominent oscillatory potentials were recorded when conditioning flashes of maximal intensity were used (log I = 0).

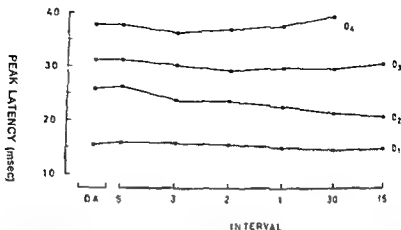


Fig 4

Peak latencies of the individual oscillatory potentials (O_1 , O_2 , O_3 , O_4) plotted against interval between stimulus flashes from ERGs shown in Fig 1a. The latency of the first, the third and the fourth oscillatory peak (O_1 , O_3 , O_4) showed no distinct change. The latency of the second peak (O_2) decreased when the interval between stimulus flashes decreases. The average error of repetitive calliper square readings was less than 0.5 msec.

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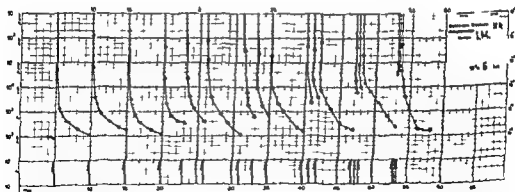


Fig 5

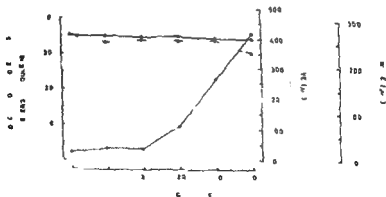
Adaptometric visual threshold in the dark after light adaptation by stimulus flashes elicited at different intervals as in Fig 1. The adaptometric curve was obtained by noting the time required for the subject to distinguish whether the test pattern at various intensities was vertical or horizontal.

was weak ($\log I_c = -5$ to -3) the electrical response resembled the ERG recorded in dark adaptation (*cf* Algere 1968) or with long interval between flashes (see present study Fig 1a). The ERG response had a large dominating first oscillatory peak which was followed by a negativity which in turn was succeeded by low amplitude indistinct oscillations. There was an increase of the oscillatory peaks when more intense conditioning flashes were used ($\log I_c = -2$ to 0).

The energy of the oscillatory potentials remained low when low intensity conditioning flashes were used ($\log I = -5$ to -3) (Fig 7). High intensity conditioning flashes ($\log I_c = -2$ to 0) induced a marked gain of energy of the oscillatory potentials.

The dominant frequency of the oscillatory potentials decreased evenly from about 150 Hz to about 110 Hz as conditioning flashes of moderate and higher intensities were used ($\log I = -3$ to 0) (Fig 8).

The implicit time of the first and the third oscillatory peak (0_1 , 0_3) did not change significantly as the intensity of the conditioning flashes increased (Fig 9). There was an increase of the latency of the fourth peak (0_4) and a decrease of the latency of the second oscillatory peak (0_2). The interval between the first and last oscillatory peak ($0_4 - 0_1$) increased about 5 msec when the intensity of the conditioning flashes increased from $\log I_c = -5$ to $\log I_c = 0$ which was also demonstrated as a decline in frequency (Fig 8) and are clearly shown on the isolated oscillation in Fig 10.



Fig

Calculated energy of the oscillatory potentials of the ERGs shown in Fig 6a and amplitudes of the a and b wave shown in Fig 6b in relation to intensity of the conditioning flashes. There was an increase in energy of the oscillatory potentials when increasing intensities of the conditioning flashes than $\log I = -3$ were used.

II INTENSITY OF CONDITIONING FLASHES

The FRG was recorded in response to the third stimulus flash of constant and maximal intensity ($\log I_s = 0$). The interval between the flashes in each series of three was 30 seconds. The first two (conditioning) flashes varied within a range of 5 log units ($\log I_c = -5$ to 0). The adaptometric visual threshold was recorded as the conditioning flashes were applied as described above.

The oscillatory potentials

The shape of the oscillatory response varied as the intensity of the conditioning flashes changed (Fig 6a). When the intensity of the conditioning flashes

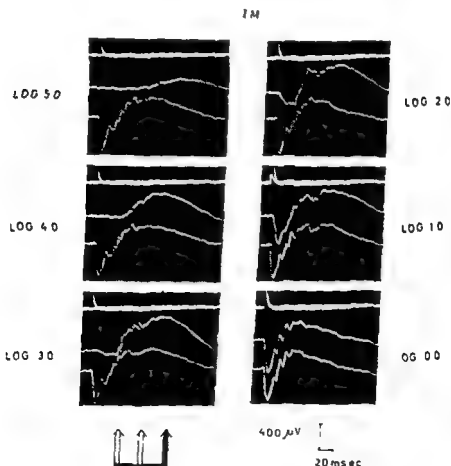


Fig 6b

Amplitudes of the m and b wave of ERG recorded in dark adaptation as in Fig 6a. Stimulation pattern as in Fig 6a.

The a-wave

The amplitude of the a wave was only insignificantly reduced as the intensity of the conditioning flashes increased (Figs 6b and 7). At the strongest conditioning light ($\log I_c = 0$) the amplitude was insignificantly depressed to about $400 \mu V$ which made up around 95% of its value in dark adaptation ($420 \mu V$).

The b-wave

The b wave was slightly depressed as the intensity of the conditioning light intensity increased (Figs 6b and 7). There was a U wave of about $230 \mu V$ recordable when the conditioning light of maximal intensity ($\log I_c = 0$) was used making up about 85% of its value in dark adaptation ($270 \mu V$).

Consequently the oscillatory and the slow potentials were differently affected by previous conditioning flashes of light. The oscillatory potentials showed a 10 fold gain of energy whereas the amplitude of the slow potentials were only slightly reduced (about 5-15%).

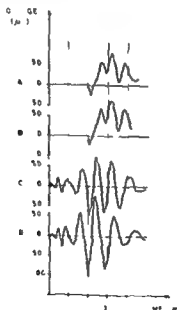


Fig 10

Oscillatory potentials recorded from the ERG's shown in Fig 6a. The ERG was recorded in response to the third stimulus flash of maximal intensity ($\log I = 0$). The intensities of the conditioning flashes were: A $\log I_c = -5$, B $\log I_c = -5$, C $\log I_c = -1$, D $\log I_c = 0$.

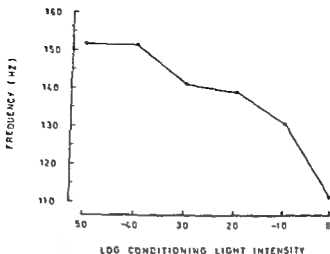


Fig 8

Dominant frequency of the oscillatory potentials of the ERGs shown in Fig 6a in relation to intensity of the conditioning flashes. There was a decrease in frequency from 152 Hz to 110 Hz as the intensity of the conditioning flashes increased.

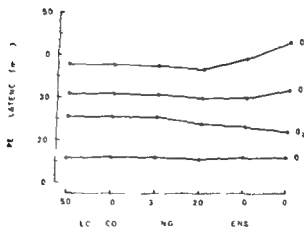


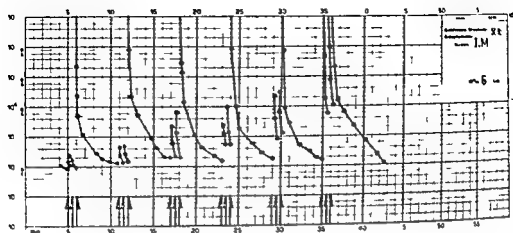
Fig 9

Peak latencies of the individual oscillatory potentials (0_1 , 0_2 , 0_3 , 0_4) of the ERGs shown in Fig 6a plotted against intensity of the conditioning flashes. The latency of the first and the third oscillatory peak (0_1 , 0_3) showed no significant change. The latency of the second peak (0_2) decreased and the latency of the fourth peak (0_4) increased when the intensity of the conditioning flashes increased. The same error of measurements as in Fig 4.

more rapid at high flash rates where it follows a suppression of the b wave of the cat's ERG (Steinberg 1966) Nagata (1969) has also demonstrated a transient oscillatory activity in the human ERG at onset and cessation of light stimulus

The short high intensity flashes used bleached a negligible amount of visual pigment (Rushton & Baker 1963 Ripps & Weale 1969) The amplitude of the a wave is only very slightly reduced (about 5-10%) when the retina is light adapted by previous flashes given at the shortest interval used (15 seconds) or when the previous conditioning flashes are of maximal intensity ($\log I = 0$) The b wave mainly photopic in nature on the other hand shows a somewhat larger reduction but decreases only about 15-20% when the strongest intensity ($\log I = 0$) or the shortest interval (15 seconds) of the conditioning flash is used The slow potentials are obviously very little influenced by the adaptation to the flashes used which also compares well with the expected insignificant reduction of visual pigment Thus the flashes in the present study which induce a certain state of light adaptation and greatly affect the energy and dominant frequency of the oscillatory potentials must be explained mainly on account of a neural process Adaptation to a weak steady background illumination may also amplify the energy and change the frequency of the oscillatory potentials when recorded at long intervals in dark adaptation This seems to be mainly mediated by a neural mechanism (Algvere & Wachtmeister 1972) Neural adaptation of the b wave has been demonstrated (Granit 1933 Arden & Granit & Ponte 1960) It is also a property of the P III component and is proposed to originate in very distal layers of retina (Dowling & Ripps 1971) and be mediated by a passive ionic diffusion (Frank 1971)

In the present study it is not easy to calculate the photochemical effect of the light flashes i.e. the exact amount of photopigments bleached formation of intermediate photoproducts etc When similar amounts of photosensitive pigments are bleached flash exposures will displace the density difference spectrum of the human retina towards longer wavelengths compared to a continuous exposure (Ripps & Weale 1969) After a short exposure to very strong light there is an initial delay of rhodopsin regeneration which was first described on rat retina by Dowling & Hubbard (1963) Similar effects have also been demonstrated in human retina (Rushton 1963 Weale 1963 1967) and by bright flashes on the cone vision in man (Rushton & Baker 1963) This delay in photosensitivity has been suggested to be caused by a competition between different products of visual pigments (Dowling & Hubbard 1963) According to Donner & Reuter (1967) the decomposition of metharhodopsin is more rapid than the synthesis of new rhodopsin which should explain the desensitizing effect of metharhodopsin This effect is more predominant after short exposures to intense light than after continuous exposures Thus a photochemical effect



D.A.

Fig 11

Adaptometric visual threshold in the dark after light adaptation by conditioning flashes of different intensities delivered at a constant interval of 30 seconds as in Fig 8. The same method of obtaining the adaptometric curve as in Fig 5.

Adaptometric visual threshold

Conditioning flashes of lowest intensity ($\log I_c = -5$) increased the sensory threshold only very slightly above the absolute threshold and the sensitivity of the rods was higher than that of the cones (Fig 11). Only when the conditioning flashes of maximal intensity ($\log I_c = 0$) were elicited was the sensitivity about 6×10^3 lux and the visual threshold given by the cone mechanism.

Discussion

From the present results it can be inferred that the oscillatory potentials seem to be strongly dependent of the state of adaptation under which they are recorded. They are more easily elicited when the interval of the successive stimuli is comparably short (less than 3 minutes) or the conditioning flashes are of stronger intensity (more than $\log I_c = -3$) and a certain adaptation to light prevails.

This is also in accordance with the concept of the oscillatory potentials being a kind of phasic potential change of the retina responding to "on" and "off" of a light stimulus which has been demonstrated on the rabbit's ERG changing stimulus intensity and interval (Yokoyama, Naka & Taniguchi 1966). The evolution of the oscillatory form of response of the optic tract is

more rapid at high flash rates where it follows a suppression of the b wave of the cat's ERG (Steinberg 1966) Nagata (1962) has also demonstrated a transient oscillatory activity in the human ERG at onset and cessation of light stimulus

The short high intensity flashes used bleached a negligible amount of visual pigment (Rushton & Baker 1963 Ripps & Weale 1969) The amplitude of the a wave is only very slightly reduced (about 5-10%) when the retina is light adapted by previous flashes given at the shortest interval used (15 seconds) or when the previous conditioning flashes are of maximal intensity ($\log I_c = 0$) The b wave mainly photopic in nature on the other hand shows a somewhat larger reduction but decreases only about 15-20% when the strongest intensity ($\log I_c = 0$) or the shortest interval (15 seconds) of the conditioning flash is used The slow potentials are obviously very little influenced by the adaptation to the flashes used which also compares well with the expected insignificant reduction of visual pigment Thus the flashes in the present study which induce a certain state of light adaptation and greatly affect the energy and dominant frequency of the oscillatory potentials must be explained mainly on account of a neural process Adaptation to a weak steady background illumination may also amplify the energy and change the frequency of the oscillatory potentials when recorded at long intervals in dark adaptation This seems to be mainly mediated by a neural mechanism (Algere & Wachtmeister 1962) Neural adaptation of the b wave has been demonstrated (Granit 1933 Arden Granit & Ponte 1960) It is also a property of the PIII component and is proposed to originate in very distal layers of retina (Dowling & Ripps 1971) and be mediated by a passive ionic diffusion (Frank 1971)

In the present study it is not easy to calculate the photochemical effect of the light flashes i.e. the exact amount of photopigments bleached formation of intermediate photoproducts etc. When similar amounts of photosensitive pigments are bleached flash exposures will displace the density difference spectrum of the human retina towards longer wavelengths compared to a continuous exposure (Ripps & Weale 1969) After a short exposure to very strong light there is an initial delay of rhodopsin regeneration which was first described on rat retina by Dowling & Hubbard (1963) Similar effects have also been demonstrated in human retina (Rushton 1963 Weale 1965 1967) and by bright flashes on the cone vision in man (Rushton & Baker 1963) This delay in photosensitivity has been suggested to be caused by a competition between different products of visual pigments (Dowling & Hubbard 1963) According to Danner & Reuter (1964) the decomposition of metharhodopsin is more rapid than the synthesis of new rhodopsin which should explain the desensitizing effect of metharhodopsin This effect is more predominant after short exposures to intense light than after continuous exposures Thus a photochemical effect

of this kind by the strong flashes used cannot entirely be ruled out but seems nevertheless unlikely to occur, since the stimulus intensity is not intense enough.

There is no simple method to separate the electrical responses to stimulus flashes into the two mechanisms reflecting scotopic and photopic processes (Granit & Munsterhjelm 1937, Motokawa & Mita 1942, Adrian 1945, Crant 1947, Armington, Johnson & Riggs 1952, Schubert & Bornschein 1952, Bornschein 1953, Alpern & Farris 1954, Burrin 1954, Armington & Thiede 1954, Auerbach & Burian 1955, Best & Bohnen 1956, François, Verriest & De Rouck 1956, Goodman & Bornschein 1957, Auerbach 1967 and many others). The stimulus flash used ($\log I_s = 0$) elicits even after 30 minutes of dark adaptation a large mixed a wave and a dominating photopic b wave in response to a single exposure. The slow process (scotopic b wave) is more prominent than the rapid photopic b wave only when light intensities about four log units below the stimulus intensities used in this study were presented. On the other hand the ERG response to the second of the conditioning flashes of different intensities reflects to a certain extent the state of the scotopic process when the interval between the flashes remained constant.

At low intensities of the conditioning light ($\log I_c = -5$ to -4) the electric responses are of the scotopic type. The oscillatory potentials have low energy and high frequency in response to the third (stimulus) flash. A conditioning light strong enough to evoke a photopic response to the second (conditioning) flash (in this study $\log I_c = -3$) induced a change in the oscillatory response to the third (stimulus) flash.

Certain prerequisite conditions seem then to be fulfilled to enable large oscillatory potentials to develop changing their frequency and energy. The threshold of the photopic b wave in response to the second (conditioning) flash has been reached and the cones are probably activated. At the time the third (stimulus) flash is delivered the sensory threshold of the sensitivity of the retina has recovered to the scotopic branch of the dark adaptation curve. The sensitivity of the rods are still higher than that of the cones. The visual threshold is determined by the cone mechanism at the time of the third (stimulus) flash only when the conditioning flashes are of maximal intensity ($\log I_c = 0$). Then after strong repetitive light stimulation the retina is organized in a photopic pattern (cf. Barlow, Fitzhugh & Kuffler 1957) and the oscillatory potentials are optimally (high energy, low frequency) recorded.

The repetitive flashes of maximal intensity ($\log I_c = 0$) induce an adaptive condition which easily elicits the oscillatory response providing the interval between the flashes is short enough. When short intervals (30 seconds and 15 seconds in the present study) are used the retinal sensitivity has recovered to the cone part of dark adaptation curve and the retinal sensitivity is deter-

mined by the cone mechanism. If longer intervals are used the retinal sensitivity has further recovered and the sensitivity of the rods are higher than that of the cones. Low frequency oscillatory potentials are recorded when the threshold of the photopic process is lower than that of the scotopic one. An oscillatory response of higher frequency is elicited when scotopic vision prevails.

The dominant frequency of the oscillatory potentials varies with the state of retinal adaptation caused by the flashes. Thus optimal oscillatory potentials of high energy and low frequency seem to be most easily elicited at a rather well defined level of retinal adaptation corresponding to the threshold for the cones. This phenomenon may be related to a reorganization of retinal pathways. Burchardt & Berntson (1972) suggested the proximal negative response closely related to the activity of the amacrine cells to be highly correlated with the laterally transmitted signals which determine the adaptive state. Thus the oscillatory potentials seem to have a characteristic behaviour similar to that of the amacrine cell response and most likely constitutes a veridical reflection of the activity of the amacrine cells. This is also in accordance with previous observations (Algvere & Westbeck 1972, Algvere, Wachtmeister & Westbeck 1973, Algvere & Wachtmeister 1979).

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oscillatory changes in the intraocular volume were pronounced. This paper deals with changes in the intraocular volume which are thought to be due to changes in the content of the vascular bed. The aims of the experiments described below are

- 1) To determine the frequency of the oscillations which will be called waves and the volume of the fluid involved
- 2) to determine the relationship between the waves and the breathing
- 3) to study the effect of nerve blockade on the wave pattern
- 4) to study the effect of changing composition of the respiratory gas on the vascular bed

Materials and Methods

Three different groups of subjects were studied (for details see ref. No. 15). Young subjects (group A) aged between 25 and 35 years. The total group contained 34 subjects. Eighteen subjects were studied in experiments with recordings of applanating force with three pressure steps and varying numbers of the total group were studied in other parts of the present investigation. Elderly subjects with normal ocular tension (group B) aged between 57 and 73 years, a number of 51 subjects. Elderly subjects with ocular hypertension without other signs of glaucoma (group C) aged between 51 and 77 years, a number of 67 subjects. In addition to these groups for special purposes some additional subjects were studied (see below).

The experiments have been carried out with an apparatus which measures continuously the applanating force and which at the same time keeps the intraocular pressure at a nearly constant and known level. The apparatus and the procedures used on living human eyes are described elsewhere (13, 14). The applanated area is calculated according to the Imbert-Fick law from the applanating force and the intraocular pressure. The displaced volume is calculated as if it was a spherical segment with a radius of 7.8 mm and the base area equal to the applanated area. Briefly the experimental procedure was as follows. With the subject in sitting position the intraocular pressure was measured repeatedly by applanation tonometry and the stabilized reading (P_i) was accepted as the intraocular pressure on which the choice of P_e was based. The above apparatus was then applied and recording of the applanating force was performed with $P_e = P_i + 6$ mmHg for three minutes. Without interruption the P_e was raised to $P_i + 10$ mmHg for another three minutes and finally a short recording with $P_e = P_i + 15$ mmHg was made (ascending pressure steps). The change in displaced volume at each change in intraocular pressure represents the volume-pressure relationship and changes in the intraocular volume occurring at constant intraocular pressure can be estimated.

Abbreviations

- P_i intraocular pressure measured by applanation tonometry final reading
 P_e intraocular pressure during the experiment

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RECORDINGS OF APPLANATING FORCE AT CONSTANT INTRAOCULAR PRESSURE

IV Intraocular volume changes due to changes in blood content

BY

WILLIAM THORBURN

Oscillatory changes in the intraocular volume of lower frequency than pulse and breathing have been observed. They were sizeable under the experimental conditions of the present study. The oscillatory waves are suggested to be due to vasomotor innervation as found in muscles but it was not possible to affect them by retrobulbar anesthesia nor by blockade of the stellate ganglion. Following inhalation of 7% CO₂ (carbogen gas) there was an almost immediate decrease in displaced volume (average 10 μ l) considered to be due to an increase in blood content of the eye. There was a negligible effect following inhalation of pure oxygen.

Key words: applanation - carbon dioxide - constant intraocular pressure - force recording - intraocular blood content - intraocular pressure - oxygen

During tonographic recording with a Schiøtz tonometer one commonly observes wave like oscillations slower than pulse and respiration. Using continuous recordings of the applanating force at constant intraocular pressure such

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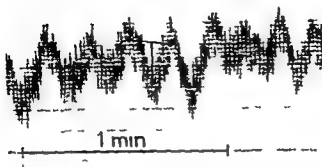


Fig 1

Example of regular waves of type 1 of a frequency of 5 cycles/min and the points which are used to calculate the corresponding change in intraocular volume (the end points of the vertical bar are the base of the calculation)

The waves were classified in three arbitrary classes according to their frequency

Type 1 Regular waves appearing at least during one minute within the frequency range of 2.1-7 cycles per minute (Fig 1)

Type 2 Regular waves with the frequency range of 0.5-2 cycles per minute (Fig 2)

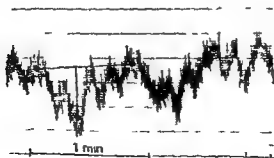


Fig 2

Example of waves of type 2 of a frequency of 1.2 cycles/min and the points which are used to calculate the corresponding change in intraocular volume (the end points of the vertical bar are the base of the calculation)

1 Recordings of applanating force with ascending pressure steps were carried out in 36 experiments on the group A in 100 experiments on the group B and in 133 experiments on the group C

2 Recordings of applanating force were performed with only one P_i level corresponding to $P_a + 6$ mmHg with simultaneous recording of the breathing by means of a temperature sensitive transducer (termistor) just in front of the nose Eight young subjects (group A) were studied

3 In five subjects not included in the groups presented above recordings of applanating force with ascending pressure steps were performed on both eyes There after two cases aged 19 and 31 were submitted to retrobulbar anesthesia of one eye In one of the cases 2 ml of mepivacain chloride (Carbocain®) 2% solution was given and complete akinesia ptosis and wide pupil occurred In the other case 1 ml of the same drug 1% solution was given and a small degree of motility remained About 90 minutes after the blockade the recording of applanating force was repeated on the eye in question In the three other cases aged between 48 and 55 10 ml of lidocain chloride anhydrazide with adrenalin (Xylocain® Exadrin®) 1% solution was injected around the right stellate ganglion In one of these subjects this was done on two occasions One to two hours later the second recording of applanating force was performed Clinical signs of the blockade with slight ptosis and miosis could still be observed The general pattern of the tracings before and after the blockade were compared

4 Nine young subjects (group A) divided into 2 groups were studied Each recording of applanating force was performed at one P_i level (10 mmHg added to the P_a) The first group breathed air for about three minutes (first period) then without breaking the recording the air was exchanged for a carbogen gas (7% CO + 90% O₂ + 73% N) which was breathed for another three minutes Then followed a second period of breathing air for further three minutes This procedure was repeated on the other eye with the difference that the carbogen gas was substituted for by pure oxygen in the midpart These experiments were repeated in reverse on the second group During all the experiments the pulse rate and blood pressure were measured by auscultation every minute In three of the subjects arterial blood was collected at the end of the inhalation of the carbogen gas and the pH and the pCO were determined by Astrup's method

Results

1 The frequency and volume of the waves

The intraocular volume change due to a wave was calculated as follows The mean applanating force (the middle of the pulse induced range) at the wave peaks was measured and the displaced volume calculated The difference in displaced volume was then calculated as illustrated in Fig 1-3 All recognizable waves in the recordings of applanating force of frequencies between 7 cycles/min and 0.5 cycles/min were noted and their frequency and volume were calculated

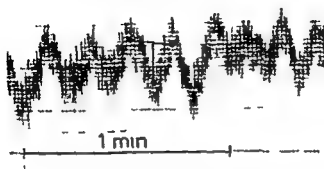


Fig. 1

Example of regular waves of type 1 of a frequency of 5 cycles/min and the points which are used to calculate the corresponding change in intraocular volume (the end points of the vertical bar are the base of the calculation)

The waves were classified in three arbitrary classes according to their frequency

Type 1 Regular waves appearing at least during one minute within the frequency range of 2-7 cycles per minute (Fig. 1)

Type 2 Regular waves with the frequency range of 0.5-2 cycles per minute (Fig. 2)

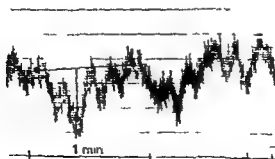


Fig. 2

Example of waves of type 2 of a frequency of 1.5 cycles/min and the points which are used to calculate the corresponding change in intraocular volume (the end points of the vertical bar are the base of the calculation)

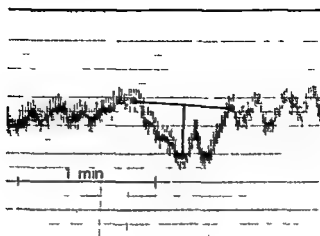


Fig 3

Example of an isolated large wave of type 3 and the points which are used to calculate the corresponding change in intraocular volume (the end points of the vertical bar are the base of the calculation)

Type 3 Isolated low frequency irregular waves (Fig 3) The difference from waves of type 2 is not distinct

In each recording of applanating force the maximum volume of each kind of wave was noted. Waves of type 1 exceeding 1 μ l were then subdivided according to their volume into three groups as were the waves of type 2 and type 3 respectively when they exceeded 3 μ l. Within the different groups of

Table 1

The occurrence of waves of type 1 (regular waves of a frequency of 2-4 cycles/min) as a percentage of all the recordings of applanating force within each group of subject

Group	Change in intraocular volume		
	1.0-5.0 μ l	5.1-10.0 μ l	> 10.0 μ l
A (n = 36)	39	42	15
B (n = 100)	56		0
C (n = 133)	69	6	2

n number of recordings

Table II

The occurrence of waves of type 2 (regular waves of a frequency of 0.5-2 cycles/min) as a percentage of all recordings of applanating force within each group of subjects

Change in intraocular volume			
Group	30-50 μ l	51-100 μ l	> 100 μ l
A (n = 36)	14	9	11
B (n = 100)	14	8	0
C (n = 133)	17	3	0

n = number of recordings

subjects each group of waves is presented as a percentage of the number of recordings of applanating force of the subject group

In all the recordings of applanating force on young subjects (group A) intraocular volume oscillations corresponding to volume changes of more than 1 μ l were observed. Waves of type 1 were present in all but two recordings with a most common frequency of five to six cycles per minute. The calculated volumes varied considerably from 1.9 to 13.9 μ l. Waves of type 2 were present in 53% of the recordings and the calculated volumes varied between 4.1 and 20.6 μ l. Waves of type 3 were present in 64% of the recordings with calculated volumes varying from 4.8 to 26.8 μ l. The results are given in Table I-III.

Table III

The occurrence of waves of type 3 (irregular and isolated waves of a low frequency) as a percentage of all recordings of applanating force within each group of subjects

Change in intraocular volume			
Group	30- 0 μ l	51-100 μ l	> 100 μ l
A (n = 36)	3	9	33
B (n = 100)	14	8	3
C (n = 133)	19	17	0

n = number of recordings

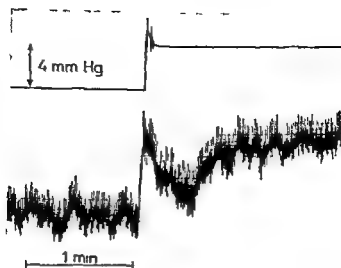


Fig 4

Temporary increase of the intraocular volume occurring after a sudden increase of the intraocular pressure by 4 mmHg

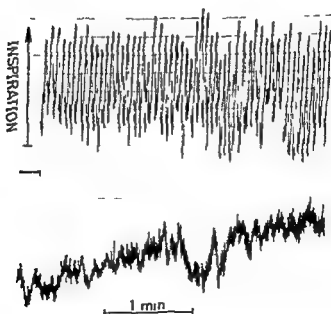


Fig 5

Simultaneous recording of breathing (upper tracing) and applanating force (lower tracing) at constant intraocular pressure

In the recordings of applanating force on elderly subjects (groups II and C) the general pattern was the same as in young subjects but the calculated volumes of the waves were on the whole smaller (Table I-III). There was no obvious difference between subjects with normal ocular tension (group B) and subjects with ocular hypertension (group C). Waves of type 1 were present in about two thirds of the recordings with a most common frequency of four to five cycles per minute.

In about one fourth of the recordings of applanating force on young subjects a different type 3 wave occurred after the intraocular pressure increase. The volume change due to this wave was sometimes very large. An example of such a wave probably induced by the intraocular pressure increase by 4 mmHg is shown in Fig. 4. The nature of this wave is not understood.

2. Breathing and waves

An example of the recording of applanating force and breathing is given in Fig. 5. The recordings were carefully examined by an independent ophthalmologist. No connection between breathing frequency and the waves of a frequency of 7 cycles per minute and less could be found in any of the recordings.

3. Nerve blockade and waves

In none of the recordings the waves disappeared. After retrobulbar anesthesia no change in the general pattern nor in the magnitude of the waves was detected. After the stellate blockade a small decrease in amplitude of the large waves and a tendency to smoother tracings was observed. It was therefore assumed that nerve blockade had little or no effect on the waves.

4. Effects due to changes in the composition of the respiratory gas

One of the recordings of applanating force during inhalation of the carbogen gas is exemplified in Fig. 6. The general appearance of the remaining eight recordings was similar. The influence of the inhalation of the carbogen gas on the intraocular volume is clearly demonstrated by the recording. Steady state levels seem to be achieved during both the first and the second inhalation of air as well as during the inhalation of the carbogen gas. The increase in intraocular volume following the commencement of inhalation of carbogen gas turned after about 80 sec to the new steady state. This time seems plausible. The somewhat shorter time between the end of the inhalation of the carbogen mixture and the new steady state during inhalation of air is compatible with a more rapid exchange of blood gases due to the deep respiration. The continuous slope of the tracing of the applanating force corresponds to the slow decrease in

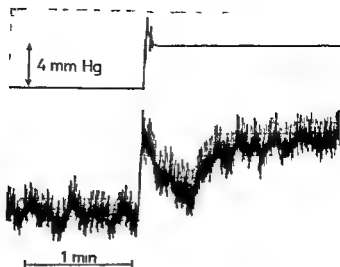


Fig 4

Temporary increase of the intraocular volume occurring after a sudden increase of the intraocular pressure by 4 mmHg

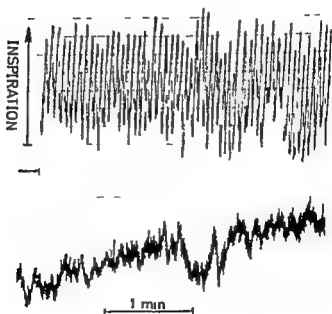


Fig 5

Simultaneous recording of breathing (upper tracing) and applanating force (lower tracing) at constant intraocular pressure

Table IV

The continuous increase in displaced volume in $\mu\text{l}/\text{min}$ during the first period of inhalation of air (a) between the first and second periods of inhalation of air (b) and during the second period of inhalation of air without the initial part (c) (cf Fig 6) The increase in intraocular volume in μl due to inhalation of the carbogen gas (d) is calculated as the difference in displaced volumes represented by the end points of the vertical arrow in Fig 6 The mean and standard error of the mean of nine subjects (group A)

	a	b	c	d
Mean	$7.2 \mu\text{l}/\text{min}$	$23 \mu\text{l}/\text{min}$	$9.0 \mu\text{l}/\text{min}$	$10.5 \mu\text{l}$
SE	0.31	0.50	0.30	1.0

ings were cut into three sections. The first contained the first period of inhalation of air and the first half minute of oxygen inhalation, the second section contained the rest of the inhalation of oxygen and half a minute of the following inhalation of air. The last section contained the rest of the second period of air breathing. Within each section the continuous increase in displaced volume was calculated in $\mu\text{l}/\text{min}$. The figures obtained are presented in Table V. The rate of increase in the displaced volume per time unit was significantly larger during the inhalation of oxygen than during the first period of inhalation of air ($p < 0.05$ sign test) suggesting a reduction in blood volume in addition to a decrease in aqueous humour content. During the inhalation of oxygen no obvious change in pulse rate nor in blood pressure was observed.

Table V

The continuous increase in displaced volume in $\mu\text{l}/\text{min}$ during the first period of inhalation of air including the initial half a minute of the following inhalation of pure oxygen (e) during the rest of the inhalation of oxygen including the initial half a minute of the second period of inhalation of air (f) and during the rest of the second period of inhalation of air (g). The mean and the standard error of the mean of nine subjects (group A)

	e	f	g
Mean	7.0	3.9	1.9
SE	0.36	0.10	0.40

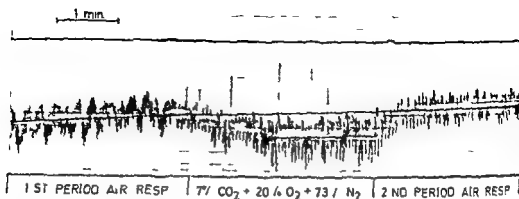


Fig 6

Recording of applanating force (lower tracing) at a constant P_t (upper tracing) during first period of inhalation of air followed by inhalation of 7% CO + 20% O + 93% N₂ and then second period of inhalation of air. The base of the calculation of the increase in the intraocular volume due to the inhalation of the carbogen gas is represented by the end points of the vertical arrow.

intraocular volume during the recording considered to be due to the aqueous humour dynamics. The shift to inhalation of the carbogen gas then resulted in an additional change in the intraocular volume thought to be due to an increase in the blood volume of the eye.

The recordings of applanating force also give the possibility of estimating the change in intraocular volume due to the increased concentration of carbon dioxide. To do this the continuous steady slope of the tracing during the first period of inhalation of air was estimated as well as that during the second period of inhalation of air after the easily distinguished effect of the carbogen gas. These two parts were connected by a line (cf Fig 6) with nearly the same slope. The continuous increase in displaced volume in $\mu\text{l}/\text{min}$ of each part was calculated. The continuous slope of the tracing during the inhalation of the carbogen gas was estimated. The vertical arrow in Fig 6 represents the change in intraocular volume due to the inhalation of carbogen gas and the ends of the arrow represents the base of the calculation. The figures obtained are presented in Table IV. During the inhalation of the carbogen gas there was an average increase in heart rate of 8 beats/min and an average increase in systolic and diastolic blood pressure of about 10 mmHg. The $p\text{CO}_2$ after about three min of the inhalation of carbogen gas was slightly increased to 41.4–49.7 and the pH was 7.29–7.31 (normal range of $p\text{CO}_2$ 32–45 and of pH 7.35–7.45).

During inhalation of pure oxygen no similar obvious change in the recordings of applanating force occurred. In order to analyse the effect the record

volume changes were made. However the pattern of the waves of the intraocular volume seems to be mainly the same as that observed in muscles.

In the present study the groups of subjects investigated showed mainly the same general pattern of waves during recordings of applanating force. However between young and elderly subjects the magnitude of the observed waves differed. Each kind of wave was larger in the young subjects than those in the elderly subjects (Table I-III). Large waves of type 3 were seen more often in elderly subjects with ocular hypertension than in those with normal ocular tension. From a physiological point of view the separation of large waves into waves of type 2 and of type 3 might well be arbitrary. In the studies of the waves of the blood flow through muscles mentioned above the possibility of age dependence is not discussed. The reason for the difference in magnitude of the waves between young and elderly subjects in the present study is not obvious. Two possibilities might be suggested. Assuming a vasomotor regulation of the waves there may be a decrease in the activity with increasing age. Possibly it might be a reduced content of the vascular bed in the elderly eye.

Possible mechanism of the waves

Autoregulation of the blood volume of the choroid has hitherto not been demonstrated. The observed oscillations of the intraocular volume (in young subjects up to 26 μ l) should result in very large oscillations of the intraocular pressure in the untouched eye. However such large changes are never observed during measurements of the intraocular pressure. This indicates that there is a pressure sensitive system regulating the content of the vascular bed of the eye which is suppressed by the constant pressure method. Such a possibility is supported among others by the results of Belmonte et al (3). They studied afferent activity in the ciliary nerves in cats and found that modifications of frequency of impulses could be obtained both with sudden and gradual increases and decreases of the intraocular pressure. A relationship seems to exist between intraocular pressure values and frequency of impulses. These results suggest the presence of specific mechanoreceptors (baroreceptors) in the eye which adapt slowly to intraocular pressure changes and that could be able also to measure ocular blood pressure reductions.

To the best of my knowledge a technique for almost excluding the pressure changes caused by pulseinduced volume changes in living human eyes has not been used previously. The evaluation of this experimental situation has thus to be made without the possibility of comparing the results with other physiological studies. It should again be stressed that the results are obtained from an experimental situation far from the normal one.

Discussion

In the present study the volume displaced by appplanation is estimated by indirect means and the figures must be regarded as expressed in a relative unit. The calculation is based on the assumption that the displaced volume is a spherical segment. This method of calculation is taken to be the lower limit value(13).

Oscillatory changes in the intraocular volume

One can only speculate upon the origin of the oscillatory changes of the intraocular volume at constant intraocular pressure described above. A likely cause is varying fluid content of the vascular bed but it is not possible to exclude other causes e.g. variations of the content of aqueous humour, changes in episcleral venous pressure or extraocular factors. Similar waves are observed during tonographic recordings with a Schiötz tonometer as reported by Becker & Friedenwald(2). They found that the slow waves noted were synchronous with phasic variations in the diastolic blood pressure. The waves observed by them were due to changes in intraocular pressure. In the present study changes in the content of the eye at artificially induced almost constant intraocular pressure are studied.

In the recordings of applating force there were slower changes than 0.5 cycles/min. It was however considered impossible to distinguish slower changes in the intraocular volume due to the content of blood from those due to changes in the content of aqueous humour. There is a fundamental difference between the eye and most other organs: a change in blood volume in the untouched eye results in a change in pressure. The present study makes use of an apparatus which almost eliminates the change in pressure which would otherwise accompany a change in the content of the eye. It is therefore of interest to see whether the reactions of the vascular bed of the eye in this experimental situation are of the same kind as those in other organs.

The general oscillating changes of blood flow through different tissues are well known. According to Matthes(11) three groups of waves of lower frequency than respiration can be distinguished: one group with 2-4 cycles per minute, one group with 0.5-2 cycles per minute and a third group with very slow changes. The blood flow through muscles varies with a frequency of about 1 cycle per minute and investigations by Hildebrandt & Golenhofen(8) and Golenhofen(7) show that the waves are synchronous in different groups of muscles and controlled by vasomotor nerves. It should be kept in mind that the blood flow in muscles was recorded directly but in the eye recordings of

volume changes were made. However the pattern of the waves of the intraocular volume seems to be mainly the same as that observed in muscles.

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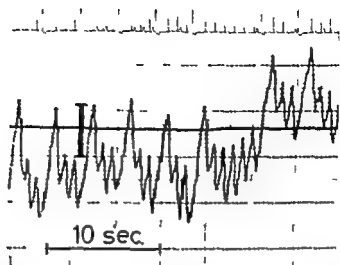


Fig 7

Recording of applanating force and ICC in a patient with heart disease and regular missed beats due to extra systoles. The base of the calculation of the decrease in intraocular volume due to the missed beat is represented by the end points of the vertical bar.

A study of a patient with heart disease gave further support to the conclusion that the large changes of the intraocular volume observed are due to changes in the content of the vascular bed. There were regular coupled ventricular extra systoles which appeared in the recording of applanating force as missed beats. The decrease in intraocular volume superimposed on the pulse induced change every time a heart beat was missed was calculated to 10-15 μ l. An example of this recording of applanating force together with simultaneous electrocardiographic recording is shown in Fig 7.

An interesting illustration of a reaction in the vascular bed of the eye was observed in a healthy subject just on the verge of fainting with tachycardia, cold sweat and pallor (Fig 5). An immediate increase in the intraocular volume considered to be due to a dilatation of the vascular bed and a change in the general pattern of the waves appeared afterwards.

Attempts to affect the waves

Previous studies of the oscillating blood flow through muscles have shown that the waves disappear when an anesthetic agent is injected around the supplying vasomotor nerves (15). No effect was however obtained when an anesthetic was injected around the stellate ganglion. It is quite possible that this blockade does not result in a complete loss of vasomotor tone. Neither was any effect found after retrobulbar anesthesia. The reason why this treatment did not

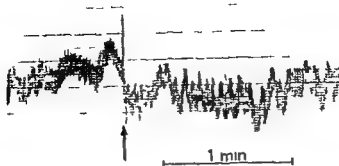


Fig 8

Record n of applanating force in a subject just on the verge of fainting (arrow) Note the immediate increase in the intraocular volume and the change in the wave pattern afterwards

affect the waves of the intraocular volume is not clear. This is compatible with an incomplete effect on the vasomotor nerves in spite of the signs of a clinical effect. The possibility still remains that the described waves and the waves of the blood flow in muscles have different origins.

Attempts to affect the Intraocular volume

The effect of a change in respiratory gas composition on retinal and choroidal circulation has been investigated by several authors (cf references listed by Andersson & McIntosh(1)). The two circulatory systems of the eye, the retinal and the choroidal, are independent and with contrasting response to changes in blood gases. In man, a constriction of the retinal vessels during oxygen breathing was observed but no significant dilatation followed inhalation of 10% CO₂ - 91% O₂ - 69% N₂ (6). No direct observations of the choroidal haemodynamics in man are reported but as the major part of the blood content of the eye is within the uvea, indirect evidence may be received by observing the intraocular pressure. Peczon et al (12) reported an increase in intraocular pressure within 2-3 min following breathing 10% carbon dioxide in oxygen. Following hyperventilation, Kaufmann et al (9) observed a decrease in the intraocular pressure correlated to the change in blood gases. In animals there is evidence of vasodilatation as an effect of increased arterial pCO₂. Flohr & Kaufmann(5) found an increase in total ocular flow positively

correlated to the $p\text{CO}_2$ in cats Trokel(16) reported an increase of both blood flow and blood content in the rabbit eye after carbogen breathing and Bill(4) found a reduced uveal vascular resistance in cats as an effect of increased pressure of carbon dioxide

Summing up the results reported in the present study (page 8) we find evidence that increased carbon dioxide exercises a dilating effect on the choroidal vascular bed in the living human eye. The observed increase in blood pressure head i.e. the increase in systemic blood pressure while the intraocular pressure was constant (page 9) might then indicate an increased blood flow through the choroid. The change in pH in the blood hardly contributes to this effect as Marcus et al (10) report a lowering of the intraocular pressure after exercise involving a simultaneous decrease of pH.

The reaction of the uveal blood vessels to changes in the oxygen content in the blood has been reported as small and inconsistent in animal experiments(4). The effect of inhalation of pure oxygen on the intraocular volume in the present study was small (Table V). A decrease in blood volume of the vascular bed of the retina (cf. above) might contribute to the result but it cannot with certainty be differentiated from a change in aqueous humour content.

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pupillary drug tests (H Stanley Thompson) 7) Physiologic tests in ophthalmology (Hansjoerg J Kolder) 8) Clinical echo ophthalmography (Karl C. Ossomig) 9) Vaso genic factors in the etiology of the field defects in glaucoma (Adnan Halasa) 10) The pathogenesis of optic nerve damage in glaucoma a review of the vascular hypotheses (Charles D Phelps) 11) Current thoughts on contact lens management (Charlotte Ann Burns) 12) Tumors of the orbit a report of 193 consecutive cases (P K Hou and M P Garg) 13) Rational use of antibiotics in ophthalmology (Bruce Golden) 14) Causes of enucleation of the eye in childhood a pathological review of 410 enucleated eyes (P K Hou) 15) Benign epithelial cysts of the eyelids (Amrit L Aurora and Frederick C Blodi) 16) An integrated system of health care and medical education (Gary M Arsham and Bruce E Spivey) 17) Information systems in ophthalmology (August Colenbrander)

P Brandstrup

Stanley C Becker Clinical Gonioscopy - A Text and Stereoscopic Atlas C V Mosby Saint Louis 1972 ISBN 0-8016-0575-X. 256 pages 940 illustrations and 119 stereoscopic views in color on 16 View Master reels with a View Master compact viewer Price US\$ 53.50

The main purpose of this excellent book is to focus attention on basic errors in present day gonioscopy which can result in misdiagnoses and critical therapeutical consequences

The commonly used gonioscopes vary widely in dimensions e.g. the corneal diameter radius the tilting of the mirror its distance from the center and its height. These differences influence the ability to look over the hill and to judge the appearance of the chamber angle. The direct application of a prism to the eye may easily result in inadvertent deformation of the cornea by suction or pressure leading to false interpretation of the nature of the angle.

The methods of gonioscopy thus are fraught with multiple defects but these defects can be completely neutralised by the author's fluid bridge method. The gonioscope is fixed to a prism holder suspended from an adjusted headband. The patient is positioned at the slit lamp as usual and the prism is narrowed down to the cornea to an interval of 2 to 3 mm. At this time saline or methyl cellulose is delivered to the interface and forms the fluid bridge. Once the bridge is formed the patient can move his eye about and still maintain the bridge or else the bridge can easily be restored while gonioscopy is in progress.

The configuration of the angle is drawn in a goniosgram with a more elaborate shading than is commonly used which the author hopes will contribute to the standardization of gonioscopic findings.

The second purpose of the book is to present both visually and in prose the chamber angle in normal variants and in pathological situations. This is achieved in a sequence of chapters dealing with glaucomas tumors traumas effects of drugs and surgery. The combined use of stereogonioscopic photographs in the view master reels provides an excellent opportunity to familiarize oneself with gonioscopic skill without the need for methodical artifacts.

P Brandstrup

JUDICIA DE NOVIS LIBRIS

Leopold Irving H (ed) Symposium on ocular therapy Vol 5 C V Mosby St Louis
1972 165 pages Price \$ 18.50

This publication records the information from the drug symposium of the American Academy of Ophthalmology in Las Vegas in October 1970. The authors are such well known authorities as Irving H Leopold Herbert E Kaufman Bernhard Becker Samuel Aronson Frederick H Theodore etc

The book gives the latest information regarding antibiotic treatment (new semisynthetic penicillins cephalosporins garamycin) different viewpoints regarding combined antibiotic and steroid therapy in keratitis and in intraocular infections new possibilities in treatment of herpes simplex discussions on prophylaxis against operative infections etc

The first chapter deals with management of inborn errors of metabolism with ocular involvement (galactosemia Nieman Pick's disease homocystinuria etc)

David Shock estimates the therapeutic possibilities in artery and venous occlusion of the retina especially plasma expanders (dextran) and intravenous urokinase

The chapters are well written and are supplemented by informative tables. The book is of interest to all who deal with therapy of the eye

M S Vorn

Olesen Ib Belysningsteknik (Lighting Technology) (text in Danish) Aschehoug Dansk Forlag Copenhagen 1972 98 pages 103 illustrations 12 tables Price Dkr 34.50

This book in standard format A4 is an up to date survey of lighting technology. It is presented as a condensation of six previous publications in the series Light and Lighting edited by the Danish Illumination Society. The plain text free of complicated formulas gives an introduction which is easily understandable by ophthalmologists without much previous knowledge of technology.

Particularly the chapter on photometric definitions and units light sources and glare calculations are of interest for the ophthalmologist who in his office often is confronted with questions on lighting and disability glare by his patients.

I Dreyer

Blodi Frederick C (ed) Current Concepts of Ophthalmology Volume III The C V Mosby Co St Louis 1972 238 pages 169 illustrations Price US\$ 9.00

Volume I of Current Concepts of Ophthalmology appeared in 1967 volume II in 1969 and volume III is as valuable and informative as its predecessors. The contributions reflect upon the activities and interest of the staff at the Department of Ophthalmology University of Iowa College of Medicine. Some are original works others summarize.

The contents of the 14 chapters: 1) Central serous retinopathy (Thomas C Burton) 2) Clinical use of iris fluorescein angiography (Ira G Wong) 3) The result of tests on a broad band filter combination for fluorescein angiography (Ogden Frazier and Lee Allen) 4) Ophthalmoscopy outline of differential diagnosis (P J Leinfelder) 5) Ophthalmic aspects of multiple myeloma (Frederick A Mausolf) 6) Diagnostic

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FUNDAL HAEMORRHAGES IN RUPTURED INTRACRANIAL ANEURYSMS

I Material Frequency and Morphology

BY

J A FAHMY

Among 19 patients with intracranial aneurysms 79 had fundal haemorrhages (FH) an incidence of 40.5% (99% confidence limits 31-50) FH occurred alone in 67% and were associated with papilloedema in 13.8% of the cases. The total incidence was found to be higher than the frequencies found by similar studies and the reasons are discussed. Among the 9 patients 33 had mild retinal haemorrhages (grade I) in 7, the haemorrhage was more severe (grade II) and 21 had preretinal or vitreous haemorrhages (grade III). Aneurysms on the anterior communicating artery with the tendency upon rupture to large haemorrhages were responsible for the greater part of FH as well as for the most severe cases (grade III) indicating a positive correlation between the amount of bleeding which suddenly occurs in the subarachnoid space and the incidence and severity of FH. No correlation could be demonstrated between the shape and site of FH and the aneurysmal site or between the laterality of FH and the hemispheric site of the aneurysm.

Key word: intracranial aneurysms - subarachnoid haemorrhage - fundal haemorrhage - retinal haemorrhage - preretinal haemorrhage - vitreous haemorrhage - frequency

Die Jahrestagung der Deutschen Ophthalmologischen Gesellschaft

wird wie stets in der letzten Septemberwoche in Heidelberg vom 23-26 September 1973 stattfinden

Hauptthema: Erkrankungen der Macula

Simultänübersetzung in Englisch und Französisch ist verfügbar Für nähere Information wende man sich an Herrn Prof. Dr. Jäger, Direktor der Universitäts-Augenklinik Heidelberg, Deutschland

International Symposium on the Eye and Systemic Disease

The Department of Ophthalmology of the University of Iowa, Iowa City, Iowa, will sponsor an International Symposium on the Eye and Systemic Disease to be held in Iowa City, November 15-17, 1973. An excellent international faculty composed of ophthalmologists, internists, and a dermatologist will discuss important practical relationships between ocular disease and systemic disease. For further information, contact Frederick A. Mausolf, M.D., Symposium Chairman, Department of Ophthalmology, University Hospital, Iowa City, Iowa 52242.

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International Symposium on the Eye and Systemic Disease

The Department of Ophthalmology of the University of Iowa, Iowa City, Iowa will sponsor an International Symposium on the Eye and Systemic Disease to be held in Iowa City November 15-17, 1973. An excellent international faculty composed of ophthalmologists, internists and a dermatologist will discuss important practical relationships between ocular disease and systemic disease. For further information contact Frederick A. Mausolf, MD, Symposium Chairman, Department of Ophthalmology, University Hospital, Iowa City, Iowa 52242.

In contrast to the material examined previously (Fahmy et al (1969) Fahmy 1970a b)) only anatomically verified cases are included in the present study. The diagnosis was established either at operation (144 cases) or autopsy (51) or both (76 cases). Out of the original series of 291 patients the following 26 were excluded: 13 patients were neither operated nor autopsied. Six patients had co-existing angioma. Two had meningioma and one had cerebral metastasis. In three patients with a history of trauma it could not be decided with certainty whether the aneurysm was congenital or traumatic. One patient with a positive angiographic finding underwent operation without any aneurysm being found.

Among the 195 patients 18 (9%) had more than one aneurysm. These patients were listed according to the ruptured aneurysms. From Fig 1 it may be seen that 13 patients had aneurysms on the anterior cerebral artery, 61 on the anterior communicating artery, 63 on the internal carotid artery, 50 on the middle cerebral artery, 3 on the basilar artery, 2 on the ophthalmic artery and 1 on the primitive trigeminal artery.

Results

Frequency

Among the 195 patients 79 had FH (40.5% - 99% confidence limits 31-50). In 50 instances the FH occurred alone (26.7% - 99% confidence limits 19-36) and in 29 cases it was associated with papilloedema (13.8% - 99% confidence limits 8-27). Fig 1 shows that FH was significantly most common in aneurysms located on the anterior communicating artery ($\chi^2 = 8.264$, $f = 3$, $P < 0.01$). Out of the 195 patients 100 were women and of these 37% had FH. Among the 95 males 42 (44.2%) had FH (Fig 2); the difference is not significant ($\chi = 1.041$, $f = 1$, $P > 0.3$). Fig 3 gives the distribution of FH by age, but the variation in the different groups is not significant ($\chi = 2.149$, $f = 5$, $P > 0.8$).

Morphology

Fundal haemorrhages may be described in respect to severity (Fahmy 1972a) shape and site.

Among the 19 patients with FH 33 had mild retinal haemorrhage (grade I), 25 had more severe haemorrhage (grade II) and 21 had large preretinal or vitreous haemorrhage (grade III).

Figs 1, 2 and 3 show the distribution of FH according to severity in respect to the aneurysmal site, sex and age.

Aneurysm on the anterior communicating artery was responsible for 11 cases out of the 21 with FH grade III, an incidence which was significant as compared to the other groups ($\chi = 3.803$, $f = 1$, $P < 0.05$). The same was true as to the 10 patients with vitreous haemorrhage (VII); 4 had aneurysm of the same

A preliminary report (Fahmy 1972a) established the incidence of fundal haemorrhages (FH) in ruptured intracranial aneurysms as 32.4%. In the present study which may be regarded as a continuation of earlier publication (Fahmy et al 1969 Fahmy 1972a b c) the incidence was reexamined and found to correspond to 40.5%. Comparing these figures with other frequencies (20% Biemond & Ter Braak (1933) 11% Richardson & Hyland (1941) 15.6% Dandy (1944) 10% Hamby (1952) 28.9% Henderson (1955)) the present study seems to show the highest incidence. One of the objects of the present investigation was therefore to find an explanation for this finding and furthermore to establish the incidence of FH in respect to the aneurysmal topographic location sex and age. Moreover it was necessary to redescribe the morphology of FH in detail and examine its relationship to the hemispheric site of the aneurysm.

Material

The material comprises 195 successive patients with ruptured intracranial aneurysms admitted to the Department of Neurosurgery S Municipal Hospital Aarhus during the period 1.4.1959 to 31.3.1970 (11 years).

Table 1

Incidence of fundal haemorrhages in ruptured intracranial aneurysm as reported by the various authors

Authors	Intracranial aneurysms	Retinal haemorrhages		Total %
		Alone %	Associated with papilloedema %	
Biemond & Ter Braak (1933)	40	15	5	20
Richardson & Hyland (1941)	118	5.1	5.9	11
Dandy (1944)	105	4.6	11	15.6
Hamby (1952)	130			10
Timberlake & Kubik (1952)	250	23.6		
Holmes (1954)	106	5.5		
Manschot (1954)	225	20		
Henderson (1955)	114	12.3	16.6	28.9
Kravenbuhl & Yasargil (1955)	136	14.7		
Ruse (1969)	92	20.6		
Present cases	195	26.4	13.5	40.5

In contrast to the material examined previously (Fahmy et al (1969) Fahmy 1972 a b)) only anatomically verified cases are included in the present study. The diagnosis was established either at operation (144 cases) or autopsy (51) or both (76 cases). Out of the original series of 221 patients the following 76 were excluded: 13 patients were neither operated nor autopsied. Six patients had co-existing angioma. Two had meningioma and one had cerebral metastasis. In three patients with a history of trauma it could not be decided with certainty whether the aneurysm was congenital or traumatic. One patient with a positive angiographic finding underwent operation without any aneurysm being found.

Among the 195 patients 18 (9%) had more than one aneurysm. These patients were listed according to the ruptured aneurysms. From Fig 1 it may be seen that 13 patients had aneurysms on the anterior cerebral artery 61 on the anterior communicating artery 63 on the internal carotid artery 52 on the middle cerebral artery 3 on the basilar artery 7 on the ophthalmic artery and 1 on the primitive trigeminal artery.

Results

Frequency

Among the 195 patients 79 had FH (40.5% - 99% confidence limits 31-50). In 52 instances the FH occurred alone (26.7% - 99% confidence limits 19-36) and in 27 cases it was associated with papilloedema (13.8% - 99% confidence limits 8-22). Fig 1 shows that FH was significantly most common in aneurysms located on the anterior communicating artery ($\chi^2 = 8.264$ $f = 3$ $P < 0.01$). Out of the 195 patients 100 were women and of these 37% had FH. Among the 95 males 47 (44.2%) had FH (Fig 2) the difference is not significant ($\chi^2 = 1.041$ $f = 1$ $P > 0.3$). Fig 3 gives the distribution of FH by age but the variation in the different groups is not significant ($\chi^2 = 2.142$ $f = 5$ $P > 0.8$).

Morphology

Fundal haemorrhages may be described in respect to *severity* (Fahmy 1972a) *shape* and *site*.

Among the 9 patients with FH 53 had mild retinal haemorrhage (grade I) 25 had more severe haemorrhage (grade II) and 21 had large preretinal or vitreous haemorrhage (grade III).

Figs 1, 2 and 3 show the distribution of FH according to severity in respect to the aneurysmal site, sex and age.

Aneurysm on the anterior communicating artery was responsible for 11 cases out of the 21 with FH grade III, an incidence which was significant as compared to the other groups ($\chi^2 = 3.903$ $f = 1$ $P < 0.05$). The same was true as to the 10 patients with vitreous haemorrhage (VH) 7 had aneurysm of the same

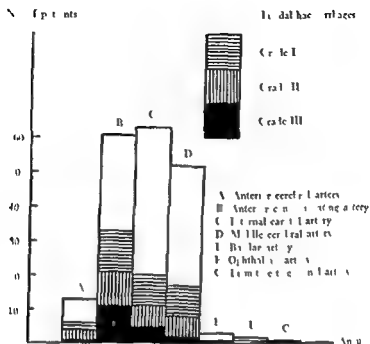


Fig 1

Incidence of fundal haemorrhages with respect to the site of the aneurysm

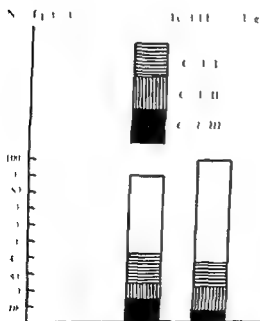


Fig 2

Incidence of fundal haemorrhages with respect to sex

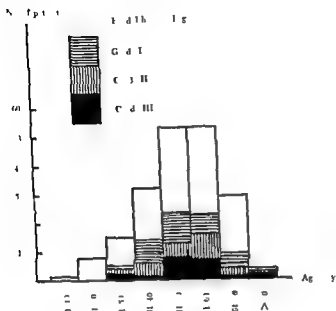


Fig 3
Incidence of fundal haemorrhages with respect to age

location. The incidence is significant ($\chi^2 = 5.233$ $df = 1$ $P < 0.025$). Additional significance could be proved in respect to sex: 9 of the 10 patients with VH were males ($\chi^2 = 5.585$ $df = 1$ $P < 0.025$). Vitreous haemorrhages were bilateral in 6 cases and unilateral in 4. As to severity, VH was massive in 6 instances, moderate in 3 and slight in 1. Seven patients died; 2 could be followed up: an ophthalmic examination 9 and 16 months later revealed a permanent visual impairment due to persisting opacities in the vitreous.

A common feature of the 10 patients was the fact that VH had arisen from a large preretinal haemorrhage which invaded the vitreous in the second week after the attack (mean time 11 days). Another feature of these patients was the tendency to large cerebral haematomas and elevated intracranial pressure as observed in 7 cases.

As to the shape of FH, retinal haemorrhages (grade I + II) were mostly linear or streaked in 32 cases, mainly round or flame shaped in 19 and combined in 7 instances. 1 preretinal haemorrhage (grade III) had a typical appearance, being more pronounced and dark. No correlation could be found between the shape of the haemorrhages and the aneurysmal site (Table II).

Table II

The shape of fundal haemorrhages in 195 patients with ruptured aneurysms (figures in brackets indicate the number of patients)

Aneurysms	Retinal haemorrhage			Preretinal haemorrhage	Vitreous haemorrhage	Total
	Linear Streaked formed	Round Flame formed	Both			
Anterior cerebral artery (13)	1	4	—	1	—	6
Anterior communicating art (61)	12	7	3	4	—	33
Internal carotid artery (63)	7	6	2	5	—	20
Middle cerebral artery (52)	11	2	2	1	1	17
Basilar artery (3)	—	—	—	—	1	1
Ophthalmic artery (2)	1	—	—	—	—	1
Primitive artery (1)	—	—	—	—	1	1
Total	32	19	7	11	10	69

Table III

The site of fundal haemorrhages in 195 patients with ruptured aneurysms (figures in brackets indicate the number of patients)

Aneurysms	Retinal preretinal haemorrhage				Vitreous haemorrhage	Total
	Papillar	Peripapillar	Peripher	Diffuse		
Anterior cerebral artery (13)	3	1	—	2	—	6
Anterior communicating artery (61)	—	3	13	—	—	33
Internal carotid artery (63)	1	5	6	9	—	20
Middle cerebral artery (52)	1	9	5	1	1	17
Basilar artery (3)	—	—	—	—	1	1
Ophthalmic artery (2)	—	—	1	—	—	1
Primitive trigeminal artery (1)	—	—	—	—	1	1
Total (195)	4	23	25	17	10	69

According to a rough classification the site of the retinal and preretinal haemorrhages was predominantly papillary in 4 cases mostly peripapillary in 25 and diffuse in 17. Table III shows that no correlation exists between the site of the haemorrhages in the fundus and the topographic site of the aneurysms.

Relationship III the hemispheric site of the aneurysm

The material was divided into three groups: 62 patients had aneurysms in the right cerebral hemisphere, 69 in the left and 64 patients on the midline. Nine patients (30.65%) of the first group, 26 (37.38%) of the second and 34 (53.12%) of the last group had fundal haemorrhages. The difference is significant ($\chi^2 = 6.899$, $df = 2$, $P < 0.05$). As may be seen from Fig. 4, no correlation could be found between the hemispheric site of the aneurysm and the laterality of FH.

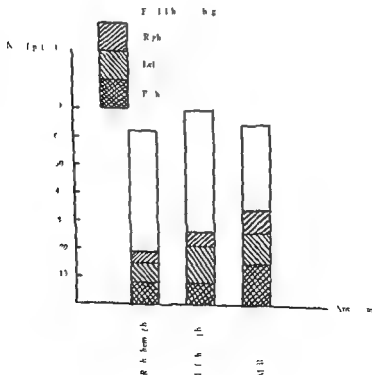


Fig. 4
Correlation between hemispheric site of the aneurysm and laterality of fundal haemorrhages

Discussion

There are several factors which may influence the establishment of the frequency of IH in ruptured intracranial aneurysms. In older literature subarachnoid haemorrhage was used synonymously with ruptured aneurysm and many authors (Biemond & Ter Braak 1933 Richardson & Hyland 1941 Manschot 1944 1954 Timberlake & Kubik 1952) selected their materials correspondingly i.e. established the diagnosis partly by lumbar puncture. Others (Holmes 1954 Henderson 1955 Krayenbuhl & Yasargil 1959 Riise 1969 Fahmy et al. 1969 1972a b) were content with positive angiographic findings. Elsewhere (Knudsen & Fahmy 1971) it was demonstrated that in some patients with a typical clinical course and positive angiographic findings the subarachnoid haemorrhage may be due to cerebral disorders other than ruptured aneurysms. Further it was shown (Fahmy et al. 1969) among 328 cases with subarachnoid haemorrhages fundal haemorrhages were significantly the most common ($P < 0.001$) in patients with intracranial aneurysms as compared with other diagnostic groups: suspicion of aneurysms, plexiform angioma and haemorrhage apoplexy. Out of these facts it may be concluded that only anatomically verified materials of ruptured aneurysms would show such a high incidence of fundal haemorrhages as in the present investigation.

A different understanding of the IH may explain the variation in the reported incidence (Table I). While some authors (Biemond & Ter Braak 1933 Richardson & Hyland 1941 Dandy Henderson 1955) state the total incidence of IH and the incidences of it occurring alone and as associated with papilloedema, others (Fahmy 1952 Timberlake 1952 Manschot 1954 Krayenbuhl & Yasargil 1959 Riise 1969) indicate the incidence only either totally or solely. Elsewhere (Fahmy 1972c) it was demonstrated that IH and papilloedema were two independent signs and therefore a total indication of FH including cases associated with papilloedema may give the truest frequency.

The time elapsing from the rupture of the aneurysm until the ophthalmologic examination may play an important role in establishing the incidence of IH. Though IH in ruptured aneurysms are not absorbed as quickly as retinal haemorrhages in the newborn, an examination within days will still reveal the greater part of the cases. A sample from the present investigation including 32 patients with papilloedema was studied (Fahmy 1972c) and showed that 26 were seen within two weeks. The same may be true for patients with FH.

The fact that aneurysms situated on the anterior communicating artery with the tendency upon rupture to large haemorrhages were responsible for the greater part of IH on the one hand and preretinal and vitreous haemorrhage on the other hand indicates a positive correlation between the amount

of bleeding which suddenly occurs in the subarachnoid space and the incidence and severity of FH

According to the results of the present study only classification of FH by severity as suggested earlier (Fahmy 1972a) would have any significance. Patients with fundal haemorrhages of the various grades have different clinical courses and prognoses. The second part of this investigation (Fahmy 1973c) should serve as a further documentation.

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FUNDAL HAEMORRHAGES IN RUPTURED INTRACRANIAL ANEURYSMS

II Correlation with the Clinical Course

BY

J A FAHMY

The occurrence of fundal haemorrhages (FH) was correlated with the various ocular and neurological signs as well as with some factors with possible relation to the intracranial pressure. A positive association was found to papilloedema ($P < 0.0005$), unconsciousness ($P < 0.005$) and cerebral vascular sclerosis ($P < 0.005$).

FH proved to be an important prognostic factor and occurred mostly among fatal cases and disabled survivors ($P < 0.0005$).

Among all patients with FH those with the severest changes (grade III) had the poorest prognosis ($P < 0.05$). This fact among others seems to justify a previous suggestion (Fahmy 1970a, 1973b) that FH classification ought to be graded according to severity.

Acta et res intracranial aneurysms - subarachnoid haemorrhage - clinical course - prognosis - fundal haemorrhage - retinal haemorrhage - pre-retinal haemorrhage - vitreous haemorrhage

This part of the present investigation attempted to correlate fundal haemorrhages (FH) with other symptoms and signs as well as with some factors taking part in the clinical course of ruptured intracranial aneurysms and furthermore to assess the prognostic role of FH and examine the value of classifying it if according to severity as suggested by Fahmy (1972a 1973b)

Material and Methods

The material is described in detail elsewhere (Fahmy 1973b) and comprises 195 successive cases of intracranial aneurysms admitted to the Neurosurgical Department S Municipal Hospital Aarhus during the period 14 1959 to 31 3 1970 (11 years). The diagnosis was purely anatomical i.e. established either at operation (144 cases) or at autopsy (51 cases) or both (26 cases). Thirteen patients had aneurysms on the anterior cerebral artery 61 on the anterior communicating artery 63 on the internal carotid artery 32 on the middle cerebral artery 3 on the basilar artery 2 on the ophthalmic artery and 1 on the primitive trigeminal artery.

Results

Correlating FH with other *ocular signs* the material was divided into two groups 79 patients with FH and 116 without. *Papilloedema* was present in 27 (34%) of the former group and in only 5 (4.3%) of the latter a difference which is highly significant ($\chi^2 = 28.181$ $df = 1$ $P < 0.0005$). *Paresis of eye muscles* had occurred in 15 patients of whom six exhibited FH (40%) whereas nine (78.6%) did not. *Visual field defects* were demonstrable in 11 patients 4 with FH (36%) and 7 without (6.0%). The difference is not significant.

Fig 1 shows the relationship between FH and the various *neurological symptoms and signs* such as headache unconsciousness neck rigidity impairment of consciousness (somnolence) hemiparesis facial palsy and aphasia. A positive correlation was found only for *unconsciousness* which was present in 64 (81%) of 79 patients with FH and in 76 (65.5%) of 116 without. The difference is significant ($\chi^2 = 4.851$ $df = 1$ $P < 0.05$). This significance was more pronounced ($P < 0.005$) when FH was correlated with the duration and severity of unconsciousness (Fig 2). Fifty-five patients had not been unconscious.

Fundal haemorrhages in ruptured intracranial aneurysms II

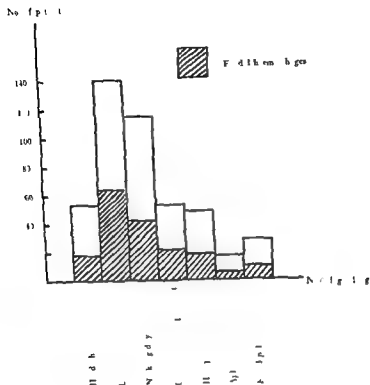


Fig 1

Fundal haemorrhages relationship to the various neurological symptoms and signs

60 for only a short time 54 for less than 24 hours 13 for more than 24 hours and 13 for more than 48 hours. The incidence of FH in the different groups was 21% 35% 46% 61% and 11% respectively. This variation was significant ($\chi^2 = 15.021$ f = 4 $P < 0.005$).

As to the relationship to factors of possible relation to the intracranial pressure intracranial haematoma around the aneurysms with or without breaking through the ventricles was present in 30 (33%) patients with FH and 34 (33%) without a difference which is not significant ($\chi = 1.597$ f = 1 $P > 0.1$). Trachnoid adhesions due to recurrent haemorrhages had occurred in 56 patients 23 with FH (29%) and 33 without (28%). Arterial hypertension (previously diagnosed) was present in 15 (19%) patients of the former group and in 17 (10%) of the latter an insignificant difference ($\chi = 2.938$ f = 1 $P > 0.1$). Angiography proved cerebral vascular sclerosis was present

This part of the present investigation attempted to correlate fundal haemorrhages (FH) with other symptoms and signs as well as with some factors taking part in the clinical course of ruptured intracranial aneurysms and furthermore to assess the prognostic role of FH and examine the value of classifying it according to severity as suggested by Fahmy (1972a 1973b)

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The material is described in detail elsewhere (Fahmy 1973b) and comprises 195 successive cases of intracranial aneurysms admitted to the Neurosurgical Department S Municipal Hospital Aarhus during the period 1.4.1959 to 31.3.1970 (11 years). The diagnosis was purely anatomical i.e. established either at operation (144 cases) or at autopsy (51 cases) or both (26 cases). Thirteen patients had aneurysms on the anterior cerebral artery, 61 on the anterior communicating artery, 63 on the internal carotid artery, 52 on the middle cerebral artery, 3 on the basilar artery, 2 on the ophthalmic artery and 1 on the primitive trigeminal artery.

Results

Correlating FH with other *ocular signs* the material was divided into two groups: 79 patients with FH and 116 without. *Papilloedema* was present in 27 (34%) of the former group and in only 5 (4.3%) of the latter: a difference which is highly significant ($\chi^2 = 28.191$, $f = 1$, $P < 0.0005$). *Paresis of eye muscles* had occurred in 15 patients of whom six exhibited FH (40%) whereas nine (78%) did not. *Visual field defects* were demonstrable in 11 patients: 4 with FH (50%) and 7 without (60%). The difference is not significant.

Fig. 1 shows the relationship between FH and the various *neurological symptoms and signs* such as headache, unconsciousness, neck rigidity, impairment of consciousness (sommolence), hemiparesis, facial palsy and afasia. A positive correlation was found only for *unconsciousness* which was present in 64 (81%) of 79 patients with FH and in 76 (65.5%) of 116 without. The difference is significant ($\chi^2 = 4.951$, $f = 1$, $P < 0.05$). This significance was more pronounced ($P < 0.005$) when FH was correlated with the duration and severity of unconsciousness (Fig. 2). Fifty-five patients had not been unconscious

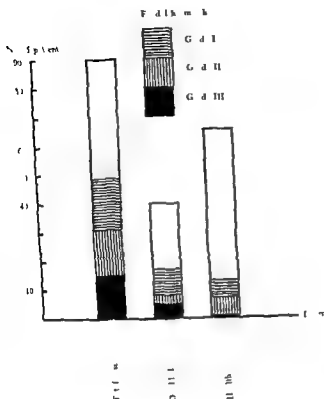


Fig 3

Fundal haemorrhages (classified according to severity) Prognostic significance

present study this association could be clinically confirmed on the basis of the significant correlation between the duration and severity of unconsciousness and the occurrence of FH. Both signs are cardinal from the diagnostic (Fahmy 1973 a) as well as the prognostic (Fahmy 1973 d) point of view.

As expected no relationship was found between the subacute intracranial hypertension which may develop in connection with the intracerebral haematoma around the aneurysms and the occurrence of FH. Nor did there seem to be a relationship with the arachnoid adhesions due to the repeated haemorrhages which may cause a communicating hydrocephalus and FH.

No one knows with certainty the time relation between rupture of the aneurysms and the onset of FH. Clinical observations (Manschot 1944, Walsh & Hoyt 1963, Fahmy (unpublished data)) as well as experimental studies (Smith et al 1955, Hedges et al 1964) suggest a simultaneous occurrence following

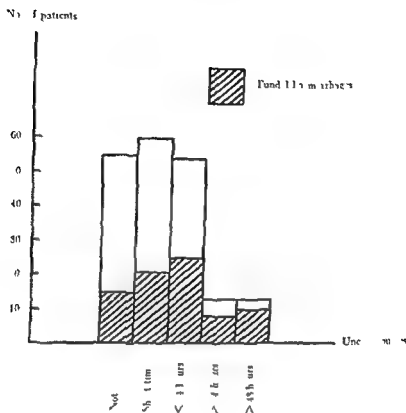


Fig 2

Fundal haemorrhages relationship to the duration and severity of unconsciousness

in a total of 75 patients 31 (41%) exhibited FH and 44 (59%) did not. The difference is significant ($\chi^2 = 6.455$ $df = 1$ $P < 0.025$).

Fig 3 demonstrates the prognostic significance of FH. The material was divided into three groups: fatal cases (90 patients), disabled survivors (40 patients), and healthy survivors (65 patients). The incidence of FH was 54.4%, 42%, and 20% respectively. The variation was highly significant ($\chi^2 = 18.64$ $df = 2$ $P < 0.0005$). Of 21 patients with FH grade III (preretinal and vitreous haemorrhage), 15 belonged to the first group, 5 to the second, and only one to the third. This variation was also significant ($\chi^2 = 4.944$ $df = 1$ $P < 0.05$).

Discussion

In the first part of this investigation (Fahmy 1973b) a positive correlation was found between the amount and extent of subarachnoid haemorrhage caused by ruptured aneurysms and the incidence and severity of FH. In the

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SPECTRAL ANALYSIS OF EMG FROM M RECTUS LATERALIS OCULI IN SUSTAINED CONTRACTIONS

BY

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EMG from skeletal muscles in sustained contractions modifies as fatigue sets in. Spectral analysis provides a sensitive tool for quantifying these changes related to muscle fibre action potential propagation velocity. In a study of m. rectus lateralis spectrum analysis revealed the same modifications related to fatigue as have been seen previously in skeletal muscles. The EMG changes were particularly pronounced at maximal voluntary deviation of the eye. It is concluded that the average fibre propagation velocity of the muscle concerned is affected by sustained lateral eye deviations.

Key words: electromyography - musculus rectus lateralis - fatigue - spectrum analysis - muscle fibres

Ever since Björk (1952) published his work on the EMG of eye muscle numerous articles concerning the practical clinical use of EMG in eye muscles have been published (Björk & Kugelberg 1953, Breinin 1969, Petersen et al 1971). The eye muscles differ in many ways from the striated muscles of the extremities. The content of connective tissue is greater than in other muscles and the vascularisation and the nerve supply is more marked in the eye muscles (Jampolsky 1970). The EMG signal is also different, the repetition frequency of the motor unit action potential being considerably higher and the

the sudden elevation of the intracranial pressure to levels above the systemic arterial blood pressure

According to the present results FH proved to be an important prognostic factor occurring mostly among fatal cases and disabled survivors ($P < 0.0005$). This finding will be evaluated and discussed in a subsequent paper.

Among all patients with FH those with the severest changes (grade III) proved to have the poorest prognosis ($P < 0.05$). This fact among others may justify the suggestion (Fahmy 1972 a 1973 b) that FH ought to be classified on a descriptive basis according to severity. Such a grading system should be used not only by ophthalmologists but also by those neuro surgeons who deal almost daily with ruptured aneurysms.

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Spectral Analysis of ocular EMG

An example of an analysis is shown in Fig. 1. The recordings are smoothed with a time constant of 1 seconds. The reason for the high variability in the 32 Hz band is the low bandwidth of the pertaining octave band filter.

Material

Signals were acquired and analysed as described above from five healthy volunteers: two males and three females. All experiments were performed according to a routine in which the EMG was first recorded for 30 seconds with the eye in a neutral straight forward position. Then the subject was asked to move the eye to an extreme lateral position and EMG was again recorded for 30 seconds. Some time after this maximal effort a recording in the neutral state was again taken in order to make sure that the spectrum had not changed markedly due to needle displacements, for instance.

In addition to this program signals from two volunteers were recorded also with the eye in intermediate positions (20 and 45 degrees lateral deviation).

Results

Fig. 1 shows a typical recording obtained in the analysis. This case also includes 20 and 45 degree lateral deviations. For clarity 60 seconds of maximal deviation are included.

The total signal level given in the bottom channel varies clearly with respect to the various eye positions. It should be emphasized that the amplitude is given in logarithmic scale. Of course in a linear scale any of the modifications would tend to be even more pronounced.

Although there are some minor fluctuations in the different bands it is seen that the spectral properties do not modify much during the 30 second recordings taken at medial deviation, neutral position and 20 and 45 degrees lateral deviation. In the case of maximal lateral deviation however there is a very marked decrease in the high frequency bands. This decrease very similar to what has been found for other muscles (Kadefors et al. 1963; Kadefors & Petersen 1970) amounts to about 6 dB in the 2000 Hz band in the example given.

Table 1 summarizes the spectral modifications obtained in the analysis. Measurements were taken at the beginning and at the end of the 30 second intervals. It is seen that the high frequency decrease is present to a variable extent in all cases and that this decrease is balanced by an augmentation in

action potential duration being shorter as compared to the EMG of an arm or leg muscle (Björk & Kugelberg 1953). The single fibre EMG reveals five different fibres in the eye muscle (Bach & Rita et al 1971). The presence of these fibres explains the different eye movements that the eye can perform such as saccades, tracking movements and microsaccades. In striated muscles from the extremities it is shown (Kadefors et al 1968) that a sustained contraction will result in a decrease in the high frequency signal components. This can be explained in various ways. In a contractile state the muscle circulation is affected with a decrease in venous outflow secondary to a stasis of the veins. The accumulation of acid metabolites such as lactic acid will affect the muscle fibres reducing the conduction velocity and thereby the content of high frequency (Mortimer et al 1970). Another explanation of this phenomenon is that different fibres in the muscle are specialized for different tasks. In sustained contraction the high frequency fibres are used only in the beginning of the contraction hence the decrease in this part of the spectrum. It could be expected in the eye muscles with their better circulation properties that no accumulation of lactic acid should take place when the muscles contract for a longer period of time. In such a case no decrease of high frequency components should be expected. However if this explanation is correct the eye muscles would react in the same way as do striated muscles.

Method

Myoelectric signals from the rectus lateralis oculi were collected by 0.4 mm diameter corvinal needle electrodes. The signals were fed through a Dist Elec tromyograph and recorded on tape using a Philips Analog 7 FM tape recorder. The recording speed was set to 30 inches per second rendering a signal band width exceeding 10 kHz.

The spectrum analysis was performed on a filter bank analyser (Ortengren 1970) allowing octave band analysis with centre frequencies 32, 125, 500 and 2000 Hz respectively. The signal content within these four bands could be displayed as a function of time simultaneously on a multi channel recorder (channels 1, 2, 3 and 4). A fifth channel indicating the total signal level was also available. The spectrum analyser can be operated in a normalizing mode in which the various filtered signals are normalized with respect to the total signal. This is the analysing mode employed in the present study. The normalization method has the advantage that the spectral contents displayed are independent of the total signal level.

Spectral Analysis of ocular EMG

Table I

spectral modifications in the various bands at maximal lateral deviation of the eye

30 s Modification (dB)				
Case no	3 Hz	195 Hz	500 Hz	2000 Hz
1	+3	+2	-1	-3
2	0	+9	-2	-6
3	0	+1	-2	-3
4	0	+2	-4	-6
5	+1	+1	-1	-9
Average	+1	+2	-2	-4

Conclusions and Discussion

The investigation showed that the spectral properties of the EMG derived from m. rectus lateralis oculi at standardized eye position can be subject to change. Such changes are consistent in the case of sustained maximal lateral eye deviations. Here the signal rms value within the 2000 Hz octave band decreased by 4 dB on the average, whereas the 195 Hz value increased by 2 dB both over 30 seconds contraction.

EMG from the muscle during neutral eye position or intermediate lateral deviation showed no consistent spectral modifications.

The results indicate that the basic spectral changes previously encountered in EMG derived from skeletal muscles in fatiguing contractions (Kadefors et al 1965; Kadefors & Petersén 1970) can also be found in the case of m. rectus lateralis oculi. It has been shown that these modifications are due chiefly to a change in the average conduction velocity of the muscle fibres (Lindström et al 1970) and that this effect is caused by accumulation of muscle metabolites secondary to ischemia caused by the high muscle contraction (Mortimer et al 1970). As the basic patterns are very similar in the present case studied and in the previous investigations, there is little doubt that this basic mechanism is important in the present case as well.

This result implies that physiological fatigue on a peripheral level is present in situations where sustained lateral eye deviations are performed. Such situations may occur as a result of, for instance, work with inappropriately designed tools or when the working man has to observe vital processes without being able to follow and compensate with head movements.

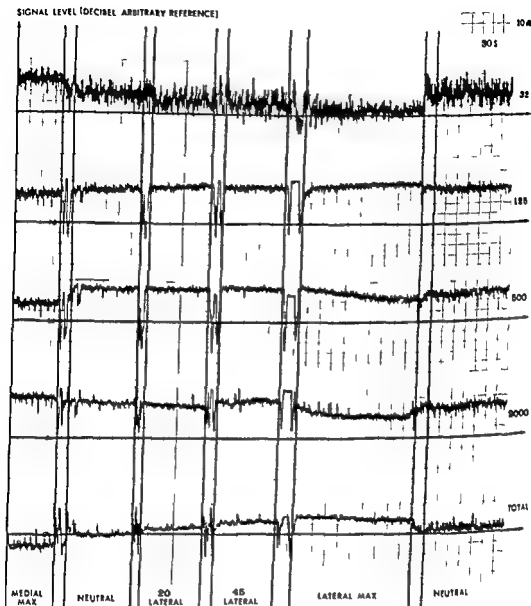


Fig 1

Analysis showing from the top activity levels (rms values) within the 92 Hz the 125 Hz the 500 Hz and the 2000 Hz octave bands as well as the total signal level FMG from m. rectus lateralis oculi in various states of contraction

the low frequency band. This gradual spectral profile modification adheres to what has previously been found for other muscles.

None of the two cases studied in intermediate eye positions showed any consistent spectral modification except for at maximal deviation.

Table I

Spectral modifications in the various bands at maximal lateral deviation of the eye

30 s Modification (dB)				
Case no	3° Hz	125 Hz	500 Hz	2000 Hz
1	+3	+9	-1	-5
2	0	+2	-2	-6
3	0	+1	-9	-2
4	0	+9	-4	-6
5	+1	+1	-1	-2
Average	+1	+2	-2	-4

Conclusions and Discussion

The investigation showed that the spectral properties of the EMG derived from *m. rectus lateralis oculi* at standardized eye position can be subject to change. Such changes are consistent in the case of sustained maximal lateral eye deviations. Here the signal rms value within the 2000 Hz octave band decreased by 4 dB on the average while the 125 Hz value increased by 2 dB both over 30 seconds contraction.

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The results indicate that the basic spectral changes previously encountered in EMG derived from skeletal muscles in fatiguing contractions (Kadefors et al 1979, Kadefors & Petersen 1970) can also be found in the case of *m. rectus lateralis oculi*. It has been shown that these modifications are due chiefly to a change in the average conduction velocity of the muscle fibres (Lindstrom et al 1970) and that this effect is caused by accumulation of muscle metabolites secondary to ischemia caused by the high muscle contraction (Mortimer et al 1970). As the basic patterns are very similar in the present case studied and in the previous investigations, there is little doubt that this basic mechanism is important in the present case as well.

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Acknowledgement

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GEOGRAPHICAL ASPECTS ON EYE DISEASES IN A SPARSELY POPULATED AREA OF NORTHERN SWEDEN

BY

ERIK LINNÉR

The influence on an eye clinic of the geographical factor of great distance was analyzed

In comparison to the number of patients living close to the eye clinic fewer patients came to the eye clinic from remote areas. The results were similar for patients with senile cataract, glaucoma and motility disturbances. Diabetics on the other hand did not show the same geographical difference. The legal requirement that an ophthalmological examination be obtained before a driver's licence will be granted in these cases was suggested as a possible explanation. The geographical barrier indicated by this study was present in spite of the fact that Social Welfare pays the patients' travel expenses and the patients themselves pay 5-10 Swedish crowns for a visit to the hospital.

Key words: distance and hospital visits - eye diseases in Northern Sweden.

Wide areas of three Scandinavian countries, Finland, Sweden and Norway, are located close to or north of the Arctic Circle. These areas are called "Nordkalotten". The population there is sparse and distances are great.

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The area where this study was made is the county of Vasterbotten. It covers about $\frac{1}{8}$ of the total area of Sweden. The distance from the coast up to the Norwegian border is more than 400 kilometres. The population is about a quarter of a million compared to 8 million inhabitants in all of Sweden.

In Umeå, about 700 km north of Stockholm, the University of Umeå was inaugurated in 1965 and already in 1959 the first group of medical students started their training. There is an eye clinic at the university hospital. In addition, one single ophthalmologist works in a hospital in Skellefteå, a city 140 km north of Umeå with about 60 000 inhabitants. That means that all eye patients in the county of Vasterbotten have to come to the clinics in Umeå or Skellefteå with their problems. Because of limited capacity, all patients except emergency cases must be referred to the eye clinic by other doctors, mostly general practitioners.

In regions with only one eye clinic and no ophthalmologists in private practice, the patients have no alternative to that clinic. The case histories in the clinic can then give some useful information concerning diseases in the whole population of the region.

This study was based on our files of case histories from inpatients and outpatients in Umeå during the last 4 years, the total number being 26 291. A representative number (7 140) chosen at random were classified according to diagnosis and an analysis was made by means of computer. The numerical calculations were made by the Computer Center of the University of Umeå.

From an ophthalmological point of view, the different case histories were classified under 13 main headings. The purpose was to use one main diagnosis for each patient as long as this heading characterized the disease in a reasonable way, but some patients had to be classified under more than one heading. Therefore the total number of diagnoses exceeds the total number of patients.

Four diagnoses were selected for further analysis: *Lens and vitreous*, the total number of patients was 604 and most of them were cases of senile cataracts in old people, 557 of these patients having been born before 1921.

Glaucoma, all different kinds of glaucoma and glaucoma suspects were included. The total number of patients was 421 and most of them were old people, 384 being born before 1921.

Motility, all different kinds of anomalies of the ocular movements were included, the most common being squint (strabismus) in children. The total number of patients was 449.

Diabetes, the total number of diabetic patients was 173. All age groups were included from 5 children under the age of 10 up to 5 patients older than 80.

Table I
Classification in terms of 111 main diagnoses

Diagnoses	Number of patients
No disease	1 115
Refractive error	1 614
Lid + adnexa	595
Conjunctiva	613
Cornea + sclera	954
Uvea	151
Lens + vitreous	604
Retina + optic nerve	873
Glaucoma	471
Motility	449
Symptomatic diagnoses	49
Injuries	110
Systemic diseases	62
All patients	7 140

years of age. They were classified according to fundus changes in pre retinopathic stage, simple diabetic retinopathy and proliferative diabetic retinopathy.

The patients under these four headings were then classified according to how far away from Umeå they were living.

The county of Västerbotten was divided into three regions according to the distance from Umeå and its eye clinic.

Central region within 30 km 63 000 inhabitants intermediate region 30–150 km 13 000 inhabitants remote region 150–400 km 43 000 inhabitants

The percentage of patients visiting the eye clinic in relation to population was calculated. The purpose was to see whether the distance from Umeå played any significant role. Concerning the frequency of eye diseases the assumption was that no essential difference existed among the populations of the three different regions.

Diseases of the lens started with 1.2% in the central region and decreased to about 0.5% in the remote region. Glaucoma showed the same tendency there was a decrease from 0.6% to 0.53%.

Most of the patients in these two groups were old people. About one third of the population was older than 50 years of age. Calculated on the basis of this old age group alone the percentage would be nearly three times as high. But

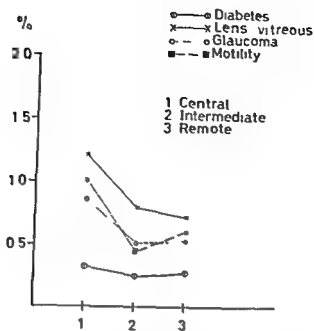


Fig 1

The influence of the distance on percentage of patients with different diseases visiting the eye clinic in Umeå. Central region within 80 km intermediate within 80-150 km and remote region within 150-400 km of Umeå

even the third group - motility - where children with squint dominated showed the same tendency the percentage of patients visiting the eye clinic decreased from 1.01 % to 0.60 %

The percentage of diabetics visiting the eye clinic was 0.32 % from the central region as compared to 0.27 % from the remote region. The proportion between the different stages did not show obvious differences related to distances from the eye clinic. The total numbers were however small.

The intermediate region was more difficult to evaluate exactly because of the ophthalmologist working outside Umeå. The number of his patients was not known nor could any clearly defined border be established for regions from which the patients chose the one or the other hospital.

Assuming that the proportion of different age groups and diagnoses of his patients were the same as among the patients coming to the eye clinic in Umeå the percentage of visits in the intermediate region seems to be approximately the same as for the central region.

Concerning cataract, glaucoma and motility disturbances the patients from the remote region who had distances of more than 150 km to the clinic were found to pay fewer visits the number being only about 60 per cent of that in

the central region. There was no obvious difference between the old age group with cataract and glaucoma and the young age group with squints. On the other hand, among diabetics the geographic differences seemed to be less marked. There is one additional factor concerning the diabetic patients in particular which might be of importance. In addition to medical reasons, the diabetics have a legal reason for visiting an ophthalmologist. According to Swedish law, an ophthalmological examination is required for a new driving licence when the diabetic disease has lasted for more than 10 years, and control examinations of diabetic eyes are also required later on.

The conclusion which can be drawn from this study is that the figures indicate a geographical barrier for patients living far away from the eye clinic, despite the fact that Social Welfare pays the travel expenses and all patients pay 5-10 Swedish crowns for a visit to the hospital.

The influence of the distance to the eye doctor as analyzed in this study is one type of investigation which is possible in a region with one eye clinic only. Other aspects concerning the panorama of disease in a population can also be studied. Although the figures can give some indication concerning the total need for medical care, it is necessary to be careful about using these figures alone as a measure in terms of absolute figures. Additional information from such other types of studies as mass surveys is needed. Assuming that the need for medical care is analyzed by using the different methods available, it might be possible to obtain information of some help in deciding the priorities of different medical fields. This type of information will be especially important in a situation where expansion is limited by rapidly increasing costs.

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HEREDITARY CRYSTALLINE CORNEAL DYSTROPHY OF SCHNYDER

BY

NIELS EHLERS and MARTIN E MATTHIESSEN

A family with three members affected by hereditary crystalline corneal dystrophy of Schnyder is reported. Penetrating keratoplasty was performed in two of the affected members. Clear grafts were obtained. The buttons were examined by light and electronmicroscopy. The epithelium was normal. In the superficial stroma deposits often of a crystalline nature were seen. Electron microscopically the deposits appeared as empty spaces either of regular geometrical form suggestive of crystals or smaller rounded and more irregular. The collagen fibrils were normal. Staining for acid mucopolysaccharides revealed no abnormalities. Adjacent to the lipid deposits were found cells which contained membrane bound granules which appeared empty or contained crystal like material. The cells were shown to contain non specific As acetate esterase and β hydroxybutyrate dehydrogenase.

It is suggested that the cells are of pathophysiological significance although their function is at present entirely speculative. Two possibilities are suggested: the cells may be concerned with removal of the deposited material or they may themselves produce the abnormal material.

Key words: cornea - crystalline dystrophy (Schnyder) - heredity - electronmicroscopy

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Corneal Dystrophy

Although known in the older literature hereditary crystalline corneal dystrophy gained recognition as a special entity as a result of work by Schnyder (1921, 1939). The literature has been reviewed by Form (1951), Delleman & Winkelmann (1968) and recently by Bron, Williams & Carruthers (1972). The disorder is hereditary with an autosomal dominant transmission. It appears as a bilateral, usually symmetrical, central discoid opacity localized in the anterior part of the corneal stroma. In the slit lamp the opacity is polychromatic, composed of innumerable small needle-like crystals and punctate opacities. There is neither vascularization nor signs of irritation of the eyes. It often begins in childhood and progresses slowly. The visual acuity is reduced to a varying degree. The corneal sensitivity is reduced.

Family K

Fig. 1 shows a family affected by hereditary crystalline dystrophy.

Case 114

(No. 151519) The proband, a 61-year-old woman, complained of visual deterioration which had progressed slowly since the age of 40. Except for a nephritis at the age of 10, she had always been of good health.

Ocular examination. Visual acuity in the right eye was 0.3 + 1.50 sph; in left eye 0.3, not improved by glasses. No xanthelasmata, normal ocular movements, pupils reacted normally to light and convergence. Corneal sensitivity was definitely diminished. Bio-microscopy revealed identical changes in the two corneae.

Central corneal thickness was normal (OD 0.51 mm, OS 0.52 mm). The corneal surface appeared completely normal with a normally displaceable precorneal film. Im-

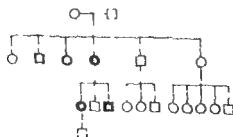


Fig. 1

Family K. (Chequered) circle = man with crystalline dystrophy and arcus lipoides. Hat = square = man with arcus lipoides but no crystalline dystrophy.



Fig 2
Case II 4 Right cornea



Fig 3
Case III 3 Left cornea

mediately beneath the epithelium and mainly localized to the anterior half of the stroma was a central rounded ringlike opacity (Fig 2) composed of innumerable minute white needle like crystals which in focal illumination might appear in different colours. Between the crystals were numerous tiny rounded non crystalline white opacities. The central opacity measured about 7 mm in the vertical and horizontal meridians. There was a heavy arcus lipoides with a peripheral clear zone. The limbal region was normal, no limbus girdle. Anterior chamber, iris and lens were normal. Applanation tonometry 10 mmHg in each eye.

General examination A clinical examination showed a normal healthy woman who neurologically (Dr V. Grynderup) revealed no signs of affection of CNS or peripheral nerves. There were no skin lesions. The electrocardiogram was within normal limits. Radiography of the thorax showed a normal heart. There was a thoracic kyphoscoliosis and osteochondrosis. ESR 5 mm/h, haemoglobin 138 and 149 g/100 ml, erythrocytes $4.2 \times 10^6/\mu\text{l}$ (mean cell volume 102 μm^3 ; mean cell haemoglobin concentration 34%), serum creatinine 0.9 mg%, serum electrolytes normal, serum proteins 6.8%. Serum cholesterol 268 mg/100 ml (normal 150–300), serum triglyceride 128 mg/100 ml (normal 50–175).

Treatment On March 22, 1971 a left 7.1 mm penetrating keratoplasty was performed. The button was fixed with interrupted sutures. Immediate postoperative course was uneventful. Topical atropine, chloramphenicol and steroid (Ultracortenol®) were given for 3 months. Sutures were removed after 6 weeks. Systemic steroids were given during the first 7 weeks. Final visual acuity 0.5–2.0 sph–3.0 120°. The transplantation was ABO compatible. Three HL A antigens were demonstrated in donor and recipient and two were identical, allowing one or two HL A incompatibilities.

Case III, 1

(No. 030137) A 34 year old healthy woman. No visual complaints. Visual acuity 10+200 sph in each eye. Central cornea thickness 0.52 mm. In both eyes slit lamp examina-

tion showed an arcus lipoides with a clear peripheral zone. The limbal region was normal. Centrally in each cornea faint crystalline deposits were seen in the anterior stroma. The changes were most pronounced in the right cornea where two small rings of crystals were found (Type F of Delleman & Winkelman (1965)).

Case III 3

(No 190347) A 94 year old man who since birth had had opacities in both corneas. There had been slight deterioration of vision during the years, never pains or infection.

Ocular examination: Visual acuity in the right eye 0.1, in the left eye 0.05. Through a pin hole he could read 0.2. Slit lamp examination revealed in each cornea a round 5 x 5 mm opacity composed of glistening crystals localized in the anterior third of the stroma (Fig 3). There was no vascularization. Central corneal thickness 0.57 mm. Reduced corneal sensitivity. Anterior chamber, iris and lens normal. Ophthalmoscopy normal.

General examination: The patient was in good health and except for a marked kyphoscoliosis verified by radiography the clinical examination revealed nothing abnormal.

Serum cholesterol 263 mg/100 ml (normal 150-300), triglyceride 135 mg/100 ml (normal 50-175).

Treatment: On February 2, 1972 a right 7.0 mm penetrating keratoplasty was made. The disc was fixed with interrupted sutures. The postoperative treatment was exactly as described in case III 4. After five weeks the thickness of the transplant was 0.54 mm and after 3 months the graft was completely clear. Two months later there was an episode of transient oedema lasting for one week. On this occasion vessels reached the edge of the graft. The oedema cleared and visual acuity with correcting glass was 0.33. Steroid medication was discontinued and 10 months after operation a typical graft rejection occurred. The graft became opaque but cleared upon systemic and subconjunctival steroid medication. Final visual acuity 0.33 with correcting glass. The transplantation was ABO compatible. Four HLA antigens were demonstrated in donor and recipient and maximum incompatibility was present.

Remaining cases

- III 1 and II 1: the parents of the proband were dead but both had had good vision. III 2 and III 3 were not examined but had no visual complaints. III 4 was hypermetropic (R) D visual acuity was 0.1 in the right eye 0.5 in the left. Slit lamp examination showed a marked arcus lipoides but no crystalline dystrophy. III 5 had visual acuity 1.0 in each eye. Slit lamp examination showed a marked arcus lipoides, no crystalline dystrophy. III 6 normal visual acuity, slit lamp examination normal. III 7 had had diabetes mellitus since the age of 20 years. Visual acuity in right eye 0.1 in the left eye 0.5-0.5 sph. Slit lamp examination normal, especially no arcus lipoides or crystalline dystrophy. Ophthalmoscopy showed proliferative diabetic retinopathy. III 8, III 9 and III 10 were said to have normal eyes. III 11 normal visual acuity, normal slit lamp biomicroscopy.



Fig 2
Case II 4 Right cornea



Fig 3
Case III 3 Left cornea

mediately beneath the epithelium and mainly localized to the anterior half of the stroma was a central rounded ringlike opacity (Fig 2) composed of innumerable minute white needle like crystals which in focal illumination might appear in different colours. Between the crystals were numerous tiny rounded non crystalline white opacities. The central opacity measured about 7 mm in the vertical and horizontal meridians. There was a heavy arcus lipoides with a peripheral clear zone. The limbal region was normal, no limbus girdle. Anterior chamber, iris and lens were normal. Applanation tonometry 10 mmHg in each eye.

General examination. A clinical examination showed a normal healthy woman who neurologically (Dr V Grynderup) revealed no signs of affection of CNS or peripheral nerves. There were no skin lesions. The electrocardiogram was within normal limits. Radiography of the thorax showed a normal heart. There was a thoracic kyphoscoliosis and osteochondrosis. LSR 5 mm/h, haemoglobin 138 and 149 g/100 ml, erythrocytes $4.2 \times 10^{12}/\mu\text{l}$ (mean cell volume 102 ml, mean cell haemoglobin concentration 34%), serum creatinine 0.9 mg%, serum electrolytes normal, serum proteins 6.9%. Serum cholesterol 268 mg/100 ml (normal 150-300), serum triglyceride 125 mg/100 ml (normal 50-175).

Treatment. On March 22, 1961 a left, 1 mm penetrating keratoplasty was performed. The button was fixed with interrupted sutures. Immediate postoperative course was uneventful. Topical atropine, chloramphenicol and steroid (Ultracortenol®) were given for 3 months. Sutures were removed after 6 weeks. Systemic steroids were given during the first 7 weeks. Final visual acuity 0.5-2.0 sph-30/120. The transplantation was ABO compatible. Three HLA antigens were demonstrated in donor and recipient and two were identical, allowing one or two HLA incompatibilities.

Case III 1

(No 030137) A 34 year old healthy woman. No visual complaints. Visual acuity 1.0-2.00 sph in each eye. Central cornea thickness 0.53 mm. In both eyes slit lamp examination

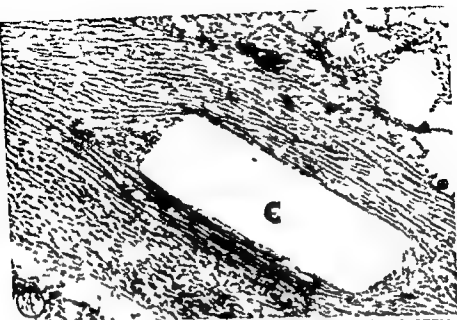


Fig. 4

Large crystal (C) in area of smaller rounded spaces. The collagen fibrils are of normal appearance. Case II-4. 45,000.

Fig. 5

Normal epithelial cell (E) with normal intracellular structures. In the stroma rounded membrane-bound spaces lying close to the basal lamina (B). 59,000.

Pathology

In 1934 Bonnet Paufique & Bonamour demonstrated the presence of birefringent ether soluble crystals in a superficial fragment of the cornea of an isolated case of crystalline dystrophy Sedan & Valles (1946) in corneal tissue from another isolated case found that the crystalline deposits dissolved in chloroform and gave positive cholesterol reactions of Salkowsky and of Liebermann Burckhardt

It is very probable that the two corneae examined were cases of Schnyder's dystrophy although heredity was not demonstrated Delleman & Winkelman (1968) demonstrated in frozen sections that the crystals gave a positive reaction of Schultz a histochemical modification of the Liebermann Burckhardt reaction

Histological studies of cases of crystalline dystrophy were reported by Malbran Prunessa & Vidal (1957) Paufique Rivault Bonnet & Laurent (1964) Delleman & Winkelman (1968) and Grop (1973) Ultrastructural studies were reported by Offret Priyru Poulouen Fure & Bisson (1966) and by Garner & Tripathi (1972)

Material and Methods The two buttons removed at transplantation were examined by light and electronmicroscopy For light microscopy tissue was fixed in ice cold formal calcium for various periods of time Various staining reactions were applied to frozen or paraffin sections as described previously (Ehlers 1970) For electronmicroscopy the tissue was cut into small pieces while immersed in 1.33° ice cold OsO_4 in 0.067 M collidin buffer (pH = 7.4) and fixed in this fluid for 3 h The specimens were then dehydrated in graded ethanol after which they were transferred to propylene oxide for 30 min and through graded mixtures of propylene oxide and Epon 812 to the embedment in Epon 812 Omission of propylene oxide in an attempt to avoid extraction of the lipids was unsuccessful One micron survey sections stained with toluidine blue formed the basis of the selection of areas for thin sectioning The thin sections (500–600 Å) were picked up on grids coated with parlodion and carbon and double contrasted with uranyl acetate and lead citrate

Observations Almost identical changes were found in the buttons from the two cases examined (II 4 and III 3) The epithelium appeared to be of normal thickness with normal intracellular structures and a normal attachment to the basal lamina In the corneal stroma areas of deposits often of a crystalline nature were seen localized mainly in the part subjacent to the epithelium but also in the deeper layers The electron micrographs showed normal collagen fibrils but their normal regular architecture was disrupted by empty spaces either of a regular geometrical form suggestive of crystals or smaller rounded and more irregular (Fig. 4) The empty spaces occasionally were close to the basal lamina (Fig. 5)

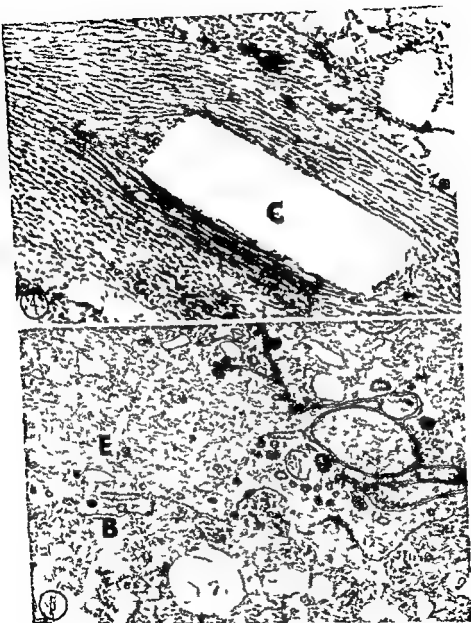


Fig 4

Large crystal (C) in area of smaller rounded spaces. The collagen fibrils are of normal appearance. Case II 4 $\times 45\,000$

Fig 5

Basal epithelial cell (E) with normal intracellular structures. In the stroma rounded clear non-membrane bound spaces lying close to the basal lamina (B) $\times 39\,000$

Pathology

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It is very probable that the two corneae examined were cases of Schnyder's dystrophy although heredity was not demonstrated Delleman & Winkelman (1968) demonstrated in frozen sections that the crystals gave a positive reaction of Schultz a histochemical modification of the Liebermann Burckhardt reaction

Histological studies of cases of crystalline dystrophy were reported by Malbran Paunessa & Vidal (1957) Pautique Rivault Bonnet & Laurent (1964) Delleman & Winkelman (1968) and Grop (1973) Ultrastructural studies were reported by Offret Payrau Pouliguen Iure & Bisson (1966) and by Garner & Tripathi (1972)

Material and Methods The two buttons removed at transplantation were examined by light and electronmicroscopy For light microscopy tissue was fixed in ice cold formol calcium for various periods of time Various staining reactions were applied to frozen or paraffin sections as described previously (Ehlers 1970) For electronmicroscopy the tissue was cut into small pieces while immersed in 1.33% ice cold OsO_4 in 0.067 M collidin buffer (pH = 7.4) and fixed in this fluid for 3 h The specimens were then dehydrated in graded ethanol after which they were transferred to propylene oxide for 30 min and through graded mixtures of propylene oxide and Epon 812 to the embedment in Epon 812 Omission of propylene oxide in an attempt to avoid extraction of the lipids was unsuccessful One micron survey sections stained with toluidine blue formed the basis of the selection of areas for thin sectioning The thin sections (500–600 Å) were picked up on grids coated with parlodion and carbon and double contrasted with uranyl acetate and lead citrate

Observations Almost identical changes were found in the buttons from the two cases examined (II 4 and III 3) The epithelium appeared to be of normal thickness with normal intracellular structures and a normal attachment to the basal lamina In the corneal stroma areas of deposits often of a crystalline nature were seen localized mainly in the part subjacent to the epithelium but also in the deeper layers The electron micrographs showed normal collagen fibrils but their normal regular architecture was disrupted by empty spaces either of a regular geometrical form suggestive of crystals or smaller rounded and more irregular (Fig. 4) The empty spaces occasionally were close to the basal lamina (Fig. 5)

DISCUSSION

From the biomicroscopical appearance and the probably dominant inheritance the three cases of the reported family can be diagnosed as Schnyder's crystalline dystrophy. A survey of the literature recently has been presented by Bron et al (1970) and in the following only pathology and pathogenetic possibilities will be discussed.

In this disorder a lipid material partly in crystalline form is found primarily in the anterior stroma. The deposits as judged from their histochemical properties are composed of or at least contain cholesterol or cholesteroesters (Sedan & Valles 1946, Delleman & Winkelman 1968, Garner & Tripathy 1970). The geometric shape of many of the empty spaces seen in the electron micrographs are compatible with the suggestion that cholesterol compounds are major constituents. The empty round spaces only allow the suggestion that they have contained some lipid material.

The cells lying in relation to the lipid deposits have not been observed previously. Offret et al (1966) described round or ovoid membrane bound structures sometimes containing osmophilic material and suggested that the vesicles were cytoplasmic organelles extruded from degenerated cells.

Probably the cells have important functions. As their origin and nature remain obscure one can at present only guess what they do. From their enzyme content and appearance in the electronmicrographs they may very well be histiocytes attempting to remove the deposited lipids. They might also be altered lipid producing stromal cells. Another possibility probably fitting with the reduced corneal sensibility would be that the cells were altered cells of Schwann producing the lipids which in this case should be abnormal myelin. The nerves in the corneal stroma are arranged in a subepithelial plexus corresponding to the primary localization of the deposits. However in the electron micrographs no definite support for this hypothesis was found.

A generalized disorder of lipid metabolism has been reported (Bron et al 1970) although in the family studied here this could not be demonstrated. The observed corneal changes are very small and develop over decades for which reason normal serum lipids cannot exclude the significance of a systemic metabolic disorder. The affected cases in the reported family all had arcus lipoides while other members (II 2 and II 3) had arcus lipoides but no crystalline dystrophy. According to Bron et al (1970) and Garner & Tripathy (1972) the corneal condition is due to a localized defect in cholesterol metabolism aggravated by systemic abnormalities in lipid metabolism. This concept is not incompatible with the findings in the presently reported family.

Adjacent to the lipid infiltrated areas cells occasionally were seen. These cells contained membrane bound granules which appeared empty or contained crystal like material (Fig. 6). Cytochemically these cells were shown to contain non specific As acetate esterase and β hydroxybutyrate dehydrogenase in tissue fixed for 3 hours and 15 minutes respectively. No reaction for alkaline naphthol AsBi phosphatase was seen in epithelium or in stroma cells after 15 minutes fixation in accordance with previous findings (Ehlers 1970). Staining with toluidine blue at various pH or with alcian blue in various concentrations of MgCl₂ revealed no abnormalities in the mucopolysaccharides of the stroma.

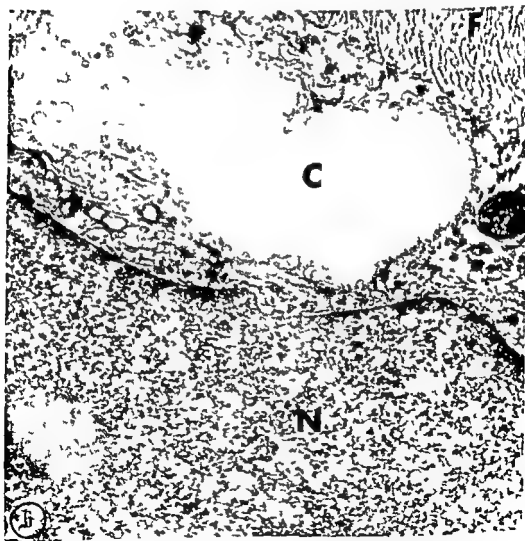


Fig. 6

Large magnification of cell in the corneal stroma with membrane bound granule in which the outline of a crystal (C) is seen. N = nucleus, F = collagen fibrils. Case III,3
 x 30 000

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OBJECTIVE MEASUREMENT OF CORNEAL SENSITIVITY

BY

MICHEL MILLODOT

This study dealt with the hitherto unresolved question of the validity of the objective method of assessing corneal sensitivity. Objective measurements were made monitoring the eye blinks while the subject simultaneously reported whether or not he felt the stimulation. A remarkably high correlation was found between objective and subjective measurements in the corneal periphery and a slightly less high one in the corneal center thus providing strong support for the use of the objective method in clinical and animal research.

Key words: cornea - sensitivity - aesthesiometer - eye blink

The sensitivity of the cornea to touch is ordinarily assessed by asking the subject whether he has felt a stimulus in contact with his cornea or to count mentally the number of times he felt the stimulus in a given set of stimulations (MilloDOT 1972). However this subjective method of investigation may be impractical with some people as for example malingerers or others who for emotional reasons or otherwise may lead the investigator to believe that he has an inordinately low touch threshold by simply replying in the affirmative at all times. Moreover the determination of corneal sensitivity on laboratory animals in either neurophysiological investigations or pharmaceutical research is not possible by this means.

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The sensitivity of the cornea to touch is ordinarily assessed by asking the subject whether he has felt a stimulus in contact with his cornea or to count mentally the number of times he felt the stimulus in a given set of stimulations (MilloDOT 1972). However, this subjective method of investigation may be impractical with some people as for example malingerers or others who for emotional reasons or otherwise may lead the investigator to believe that he has an inordinately low touch threshold by simply replying in the affirmative at all times. Moreover, the determination of corneal sensitivity on laboratory animals in either neurophysiological investigations or pharmaceutical research is not possible by this means.

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Objective Measurement of Corneal Sensitivity

filament was moved slowly toward the cornea by turning one of the knobs until it just touched the cornea as evinced by the slightest visible bend of the nylon wire. This observation was facilitated by having an $\times 4.5$ magnifier situated at right angles to the plane of the cornea. The aesthesiometer was adjusted so that the nylon wire was directed perpendicularly to the corneal point to be stimulated.

The eye blink reflex of the other eye was monitored and served as the objective criterion of corneal touch. To prevent disturbing the subject's vision, a beam of infra red light (produced by Wratten Filter no. 89 B) illuminated the eye. A photoresistor cell and lens system (Texas Instruments LS 400) sensitive in the infra red region received the light reflected by the cornea and the eyelid. The photocell was aimed at the upper eyelid so that any slight movement of the eyelid would alter the amount of light reflected and a potential difference would be engendered by the photoresistor cell. The output was fed and amplified by a sensitive strip chart recorder (Hewlett Packard 650M) which displayed the eye blink as well as the timing of the corneal stimulation. At the instant the nylon wire was placed in contact with the cornea, the operator pressed a foot pedal switch which activated the event marker of the strip chart recorder.

SUBJECTS

Twenty-five subjects between 21 and 31 years of age participated in this experiment (13 females and 12 males). Six of them wore contact lenses. All were free of ocular pathology.

PROCEDURE

The subject placed his head upon a chin and head rest. He was instructed to fixate one of various fixation points 2 meters away depending upon the corneal point to be stimulated. He was further instructed to push a button which activated a bell whenever he felt that his cornea had been touched instead of replying verbally as this would have moved his head and impaired the adjustment.

The experiment was carried out only when the humidity in the room was between 90 and 95 per cent so that the nylon filament which is affected by humidity always had about the same straightness (Millodot & Larson 1967). The measurements were begun with the longest nylon filament (that is the least pressure). A minimum of 10 readings was done for each length of the wire. Between each contact a few seconds elapsed but the frequency of the stimulation was variable. Each time the subject activated the cell the experimenter wrote a 'yes' code on the chart paper. Throughout the run a few blanks were made; the same procedure was employed as for any other stimulation.

Except that the nylon filament was brought only within a few millimeters of the cornea and then retrieved. Blanks and no subjective responses were also noted on the chart paper. These blanks were made to test the subject's reliability. The nylon filament was then progressively reduced by a half centimeter decrement and the measurements repeated until the subject responded 'yes' to most of the stimulations at a particular length.

The subjective corneal touch thresholds were determined by assessing the length of

The objective measurement of corneal sensitivity offers a valuable and sometimes exclusive technique for evaluating corneal sensitivity. It consists of eliciting a blink reflex by touching the cornea with a stimulus of sufficient pressure. If the pressure is below threshold no sensation is felt and no synchronized blink reflex should occur. This may not always be the case as seen in an instrument approaching one's eye might be sufficient stimulus to induce a blink reflex at least at the beginning of the experiment. Thus great care has to be taken in these measurements: the stimulation of peripheral corneal points where vision is greatly reduced helps to minimize this problem. Moreover the simple observation of the subject's eye while carrying out the objective measurements may be somewhat inaccurate since many observations are necessary to assess the threshold and the operator may himself be blinking and thus fail to see the subject's response. This method though has been used to determine the corneal sensitivity of animals (Regnier 1923; Strughold 1930; Darraspen et al 1964) or in experimenting with an airstream technique (Goldberg 1943) and particularly Sédan and his collaborators have made use of it systematically on their patients (Sédan, Farnier & Ferrand 1958; Morganroth & Richman 1969). However it is not known whether the objective measurement of corneal sensitivity by means of the blink reflex is valid and how accurate it is as a systematic comparison with the subjective method is still unknown. The purpose of this study is to compare the subjective corneal touch threshold with the objective threshold using an accurate and simple technique of monitoring the subject's eye blinks.

Material and Method

APPARATUS

The stimulation of the cornea was made with the Cochet Bonnet Aesthesiometer which is based upon the instrument devised by Boberg & Ans (1956). It consists of a nylon monofilament 0.12 mm in diameter which may be varied in length so that the pressure applied against the cornea may range from 11 mg to 201 mg/0.0113 mm. There exists another model of this aesthesiometer which has a monofilament 0.05 mm in diameter which may be varied in length so that the pressure may range from 2 m to 90 mg/0.007 mm, and it was also used in this experiment to produce pressures below the range of the first instrument.

The aesthesiometer was mounted in a holder which could displace it in the x, y and z axes by means of three knobs. The use of such a mechanism gave great reliability in the stimulation of a given corneal point and permitted the operator to exercise approximately the same speed of application of the nylon wire onto the cornea, a factor noted to influence the results (Boberg & Ans 1956). To get a measurement the nylon

Objective Measurement of Corneal Sensitivity

filament was moved slowly toward the cornea by turning one of the knobs until it just touched the cornea as evidenced by the slightest visible bend of the nylon wire. This observation was facilitated by having an $\times 4.3$ magnifier situated at right angles to the plane of the cornea. The aesthesiometer was adjusted so that the nylon wire was directed perpendicularly to the corneal point to be stimulated.

The eye blink reflex of the other eye was monitored and served as the objective criterion of corneal touch. To prevent disturbing the subject's vision a beam of infrared light (produced by Wratten Filter no. 89 B) illuminated the eye. A photoresistor cell and lens system (Texas Instruments LS 400) sensitive in the infrared region received the light reflected by the cornea and the eyelid. The photocell was aimed at the upper eyelid so that any slight movement of the eyelid would alter the amount of light reflected and a potential difference would be engendered by the photoresistor cell. The output was fed and amplified by a sensitive strip chart recorder (Hewlett Packard 68041) which displayed the eye blink as well as the timing of the corneal stimulation. At the instant the nylon wire was placed in contact with the cornea the operator pressed a foot pedal switch which activated the event marker of the strip chart recorder.

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The experiment was carried out only when the humidity in the room was between 70 and 90 per cent so that the nylon filament which is affected by humidity always had about the same straightness (Millo-dot & Larson 1967). The measurements were begun with the longest nylon filament (that is the least pressure). A minimum of 10 readings was done for each length of the wire. Between each contact a few seconds elapsed but the frequency of the stimulation was variable. Each time the subject activated the cell the experimenter wrote a "yes" code on the chart paper. Throughout the run a few blanks were made the same procedure was employed as for any other stimulation except that the nylon filament was brought only within a few millimeters of the cornea and then retrieved. Blanks and no subjective responses were also noted on the chart paper. The blanks were made to test the subject's reliability. The nylon filament was then progressively reduced by a half centimeter decrement and the measurements repeated until the subject responded yes to most of the stimulations at a particular length.

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The eye blink reflex of the other eye was monitored and served as the objective criterion of corneal touch. To prevent disturbing the subject's vision, a beam of infra red light (produced by Wratten Filter no. 89 B) illuminated the eye. A photoresistor cell and lens system (Texas Instruments LS 400) sensitive in the infra red region received the light reflected by the cornea and the eyelid. The photocell was aimed at the upper eyelid so that any slight movement of the eyelid would alter the amount of light reflected and a potential difference would be engendered by the photoresistor cell. The output was fed and amplified by a sensitive strip chart recorder (Hewlett Packard 680M) which displayed the eye blink as well as the timing of the corneal stimulation. At the instant the nylon wire was placed in contact with the cornea, the operator pressed a foot pedal switch which activated the event marker of the strip chart recorder.

SUBJECTS

Twenty five subjects between 21 and 31 years of age participated in this experiment (11 females and 14 males). Six of them wore contact lenses. All were free of ocular pathology.

PROCEDURE

The subject placed his head upon a chin and head rest. He was instructed to fixate one of various fixation points 9 meters away depending upon the corneal point to be stimulated. He was further instructed to push a button which activated a bell when ever he felt that his cornea had been touched instead of replying verbally as this would have moved his head and impaired the adjustment.

The experiment was carried out only when the humidity in the room was between 90 and 95 per cent so that the nylon filament which is affected by humidity always had about the same straightness (Millodot & Larson 1967). The measurements were begun with the longest nylon filament (that is the least pressure). A minimum of 10 readings was done for each length of the wire. Between each contact a few seconds elapsed but the frequency of the stimulation was variable. Each time the subject activated the cell the experimenter wrote a "yes" code on the chart paper. Throughout the run a few blanks were made; the same procedure was employed as for any other stimulation except that the nylon filament was brought only within a few millimeters of the cornea and then retrieved. Blanks and no subjective responses were also noted on the chart paper. The blanks were made to test the subject's reliability. The nylon filament was then progressively reduced by a half centimeter decrement and the measurements repeated until the subject responded yes to most of the stimulations at a particular length.

The subjective corneal touch thresholds were determined by assessing the length of

the wire at which the response was felt for 50 per cent of the number of the stimulations. This length was converted into pressure using the calibration curve of the instrument relating length and pressure which had been established previously (Milodot 1969).

The objective determination of the corneal touch threshold was done by recording on the chart paper the number of blinks which were synchronized with (or occurred within one second of) the stimulation. The objective threshold was defined as the length of the wire for which the eye blinked for 50 per cent of the number of stimulations. The subjects were not actually told that their eye blinks were monitored in order to prevent any possible conditioning to the movement of the aesthesiometer approaching their eye. The subjective and objective measurements were made simultaneously and thus the same corneal point served for both. The testing was done on a peripheral corneal point at 6 o'clock two millimeters away from the limbus for the 25 subjects. On 12 (7 females, 5 males) of these the testing was also performed on the center of the cornea.

Results

Data from a typical run of measurements gathered by stimulating the peripheral corneal point are shown in Fig. 1. The upper trace displays the monitoring of

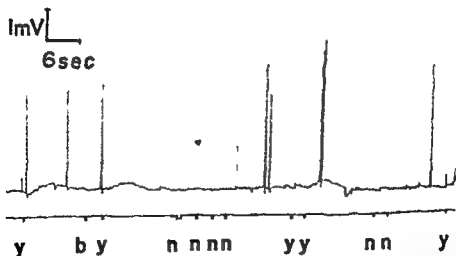


Fig. 1

Typical trace of eye blinks obtained when stimulating the periphery of the cornea. The lower line marks the various moments of stimulation. The paper unfolds from left to right. y indicates a yes response when the subject feels the touch, n a no response, b a blank.

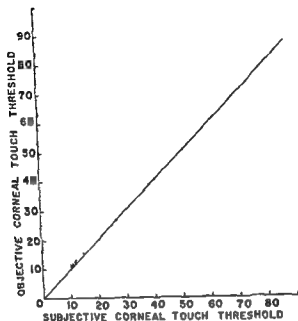


Fig. 9

Relation between subjective and objective touch threshold in the periphery of the cornea of 20 eyes. The line is equal to $y = x$ and $r = 0.99$ $P < 0.001$

the eye blinks which appear as vertical spikes. The lower trace indicates the corneal stimulations and the blinks. The various subjective responses are given for that example. One notes that the eye blink may not necessarily be covering the whole eye each time and in this display on two occasions the yes response is accompanied by only a partial blink traced as a small upward deflection. Most yes responses though are followed by a full eye blink identical to those spontaneous eye blinks unrelated to the stimulations. In this example there is no event of a blink occurring synchronously with a no response to the stimulation although such events did occur. Moreover in most subjects there were also a certain number of instances in which a yes response was not followed by an eye blink when the peripheral corneal point was stimulated. Both of these discrepancies constitute errors in the assessment of the objective touch threshold. Since these errors cause either an overestimation (a blink occurring with a no response) or an underestimation (no blink occurring with a yes response)

the wire at which the response was felt for 50 per cent of the number of the stimulations. This length was converted into pressure using the calibration curve of the instrument relating length and pressure which had been established previously (Milodot 1969).

The objective determination of the corneal touch threshold was done by counting on the chart paper the number of blinks which were synchronized with (or occurring within one second of) the stimulation. The objective threshold was defined as the length of the wire for which the eye blinked for 50 per cent of the number of stimulations. The subjects were not actually told that their eye blinks were monitored in order to prevent any possible conditioning to the movement of the aesthesiometer approaching their eye. The subjective and objective measurements were made simultaneously and thus the same corneal point served for both. The testing was done on a peripheral corneal point at 6 o'clock two millimeters away from the limbus for the 25 subjects. On 12 (7 females 5 males) of these the testing was also performed on the center of the cornea.

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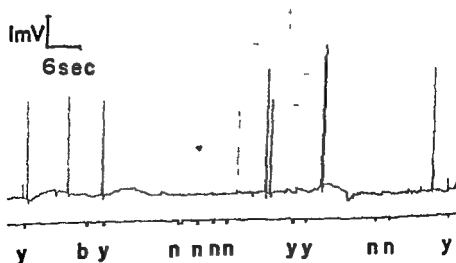


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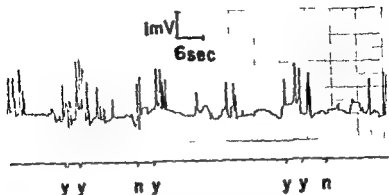


Fig 5

Typical trace of eye blinks obtained in stimulating the center of the cornea. The lower line marks the various instants of stimulations. The paper unfolds from left to right. y indicates a yes response when the subject feels the touch. n a no response.

the eye a fact known to affect the central measurement but not the peripheral one since this retinal image of the instrument is too blurred to affect the patient (Bonnet & Millodot 1966). The greater frequency of blinks contributes toward a lower objective than subjective touch threshold. This is indeed what happens for all subjects except one as is shown in Fig 4. The mean subjective corneal touch threshold for the 12 subjects was 8.54 mg/a (median 7 mg/a) and the standard deviation 4.12. The mean objective value for the same group was 4.75 mg/a (median 6 mg/a) and the standard deviation 3.86. The difference between the two means values is not significant ($t = 0.80$, $P > 0.20$). The correlation coefficient of the two sets of measurements was +0.97 which is also remarkably high and significant ($P < 0.001$).

In this case the situation is reversed as it is the objective threshold which is slightly lower than the subjective. With such a high correlation coefficient it is also possible to predict one threshold knowing the other. Given the objective threshold (Y) one can predict the subjective threshold (X) by means of the following regression equation:

$$X = 1.07(Y - 7.25) + 8.54$$

and similarly to predict Y knowing X the equation becomes

$$Y = 0.90(X - 9.54) + 7.25$$

of the objective touch threshold their effect tended to partially cancel one another and the objective threshold was found to be very close to the subjective touch threshold. Nevertheless in most subjects the objective corneal touch threshold was found to be somewhat higher than the subjective threshold as can be seen in Fig. 2. In two subjects it was the reverse. These two seemed to remain more apprehensive throughout the test unlike most other subjects as evidenced by their number of blinks. Four other subjects had exactly equal subjective and objective thresholds. Of the three least sensitive persons (highest threshold) two wore contact lenses. The mean subjective corneal touch threshold for the 25 subjects was found to be 30.78 mg/a and the standard deviation 2.5. The mean objective corneal touch threshold for the same group was 34.94 mg/a and the standard deviation 2.81. The difference between these two mean values is not significant ($t = 0.28$, $P > 0.5$). This variation in threshold across subjects is commonly found and for that reason the median is a more relevant measure of central tendency: the subjective and objective median thresholds were 25 and 28 mg/a respectively.

The coefficient of correlation for the two measurements is $r = +0.99$ which is remarkably high and significant ($P < 0.001$). This means that knowing the value of the objective threshold the subjective threshold can be predicted accurately using the regression equation $\bar{X} = R \frac{S_X}{S_Y} (Y - M_Y) + M_X$ where \bar{X} is

the objective threshold, \bar{Y} the subjective threshold, R the correlation coefficient, S_X and S_Y the standard deviation of the subjective and objective threshold and M_X and M_Y the respective means. Using the values of each symbol the equation becomes

$$\bar{X} = 0.81 (\bar{Y} - 32.94) + 30.78$$

To predict \bar{Y} given \bar{X} the same analysis yields the following regression equation

$$\bar{Y} = 1.10 (\bar{X} - 30.78) + 32.94$$

This latter is also the equation of the line which best fits the data in Fig. 2. This line has not been drawn but only the line $y = x$ which makes it easier in this instance to reveal how slight the discrepancy is between the data and the line of perfect coincidence between the objective and subjective touch threshold in the periphery of the cornea.

Data from a typical run collected from the stimulation of the corneal center are shown in Fig. 3. For most subjects the amount of eye blinks was greatly increased compared to the stimulation of the peripheral corneal point. This is caused by the apprehension brought about by the aesthesiometer approaching

Objective Measurement of Corneal Sensitivity

Millodot (1966) They had further shown that in the peripheral cornea there was no difference in threshold under room illumination and under infra red light (in the latter the patient was prevented from seeing the aesthesiometer) The results of the present study in the corneal periphery are unaffected by apprehension Moreover in most subjects there is even a slight tendency to blink less than expected on the basis of the subjective response This might be due to the fact that although the pressure is not great enough to trigger a protecting palpebral reflex it was nevertheless felt by the subject Alternatively it could be that some of these stimulations were so slight that they were barely felt whereas other stimulations with the same pressure were clearly felt and these latter were always followed by an eye blink Many subjects noted this difficulty in deciding whether they actually felt the stimulation or not Hence the discrepancy might be caused by some variability in the subjective response Nonetheless the subjective response represents the criterion against which the objective measurements are compared and it is considered the most valid psychophysical method of assessing corneal sensitivity The present results also display the well known fact that the sensitivity (threshold ¹) is greater at the center of the cornea than near the limbus (Boberg Ans 1956 Millodot & Larson 1969)

The correlation between the two procedures is so high that using the objective method on patients and on animals (in which it is the only one available) is the most feasible especially in the corneal periphery To be exact the objective data need to be corrected using the appropriate equation given above The objective method is somewhat more variable for the central measurements as some subjects particularly the nervous ones blink a great deal more than do others when the aesthesiometer approaches their eye The objective measurement of the upper part of the cornea requires in most cases that the eyelid be lifted and the experimenter must therefore observe the eye blink of the other eye which may be somewhat more cumbersome than simply using the subjective technique unless the eye blinks are monitored as in this experiment

The instrumentation used here is relatively simple and inexpensive The monitoring of the patient's eye by means of a photocell system is totally unobtrusive compared to the use of skin electrodes It is also preferable to the operator's observations as it is easier and more accurate and the operator's attention need be placed only upon the corneal stimulation Moreover it is sometimes impossible for the operator to note the subject's eye blink if he himself blinks at that same instant The mounting of the aesthesiometer on an adjustable apparatus also contributes to the precision and facility of the measurement and thus avoids many of the difficulties otherwise encountered when holding the instrument by hand

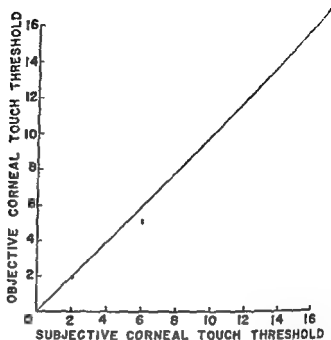


Fig. 4

Relation between subjective and objective touch threshold in the center of the cornea of 12 eyes. The line is equal to $y = x$ and $r = 0.9$; $P < 0.001$.

This latter is the equation of the line which best fits the data of Fig. 4. This line has not been drawn but only the line $y = x$ which makes it easier in this instance to reveal how slight the discrepancy is between the data and the line of perfect coincidence between the objective and subjective touch threshold in the center of the cornea.

Discussion

The results of this experiment demonstrate a basic difference between the measurements of corneal sensitivity made in the center and in the periphery of the cornea. The larger number of eye blinks occurring while measuring in the center corroborate the noted effect of apprehension demonstrated by Bonnet &

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LATTICE DYSTROPHY OF THE CORNEA

Its connection with preceding episodes of crystals and with
subsequent amyloidosis

BY

NANNY KAUNISTO

Before permanent corneal changes originate in lattice dystrophy of the cornea there are episodes with transient appearance of crystals in the cornea bulbar conjunctiva especially in the basement membrane of the epithelium and the aqueous. The shape of the crystals and a positive Adams and Sloper's performic acid Alcian blue staining reaction in the bulbar conjunctiva indicate cystine or cysteine. Two groups of patients not consanguineous were studied (Group A consisted of 25 patients group B of 9). The disease had an autosomal dominant mode of inheritance in both groups. The disease picture in group A differed clearly from that in group B as to age at onset of the symptoms intensity and duration of the episodes of the disease degree of damage to the corneal epithelium and number and quantity of general symptoms. A part of the patients in group B developed amyloidosis at age 50 or later. The observations suggest that lattice dystrophy is a sequel of a disturbance of (cystine) metabolism and amyloidosis is a secondary phenomenon. Dystrophic streaks in the cornea at least in part are injured ciliary nerves.

Key word: corneal dystrophy - lattice dystrophy - metabolism - cystine - amyloidosis

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1971 Bowen et al 1970 Meretoja & Teppo 1971 Meretoja 1972 François & Fehér 1972 Klintworth (1967) and Bowen et al (1970) consider amyloid to be strong evidence that what is involved in lattice dystrophy of the cornea is a metabolic disturbance. François & Fehér (1972) stated that the primary lesion of lattice dystrophy is a genetically determined disturbed cell metabolism and that the keratocytes produce amyloid fibrils besides or instead of collagen fibrils. According to Malbran (1912) a complicated metabolic disorder with among other things free amino acids precedes amyloid in lattice dystrophy of the cornea.

Many investigators describe recurring acute painful episodes in lattice dystrophy: they may begin in childhood (e.g. Dimmer 1899, Schappert-Kimmsjer 1933, Nemeth 1935, Standsbury 1948, Etienne 1949, Ramsay 1957, Dark & Thomson 1960 etc). Erosions or ulceration in the cornea generally are reported in connection with the acute episodes.

The purpose of this investigation was to study an unknown hereditary eye disease which is manifested as acute episodes reminiscent of iritis or scleritis (group A). Since it soon became apparent that lattice dystrophy of the cornea developed in the late stage of this disease, various phenomena associated with lattice dystrophy were studied.

Material and Methods

Two groups of patients (A and B) in my series are described in detail here. A small proportion of the patients came from the Ophthalmologic Outpatient Department, University Central Hospital, Helsinki, and from my private practice. The majority were from the Ophthalmologic Department, Kivela Hospital, City of Helsinki. The longest follow-up period was 26 years.

Because of the similarity in the clinical pattern of the eye disease, I searched for a common lineage for the patients by interviewing them, collecting data from the population register, congregational registers and provincial archives, and by researching genealogical data in the State Record Office, both personally and with expert assistance. Most of the genealogical tables were studied back to the 17th or 18th century, as far back as information was available in documentary sources. It was established that no consanguinity existed among the patients of groups A and B within at least the past 500 years.

I studied healthy relatives of the patients: 10 in group A and 13 in group B. I also made a special study of the case reports (not included in this material) of relatives of group B patients who obviously had the same disease.

A Haag-Streit 900 corneal microscope was used for the slit lamp examinations.

Biopsy specimens were taken from the bulbar conjunctiva during an attack of the disease when crystals were seen in the aqueous. The specimens were fixed in absolute alcohol and embedded in paraffin. The sections were examined unstained with a

Slit lamp examination in lattice dystrophy of the cornea reveals criss crossing and branching glassy or greyish streaks in the anterior part of the corneal parenchyma. A substance of the same appearance is seen between these streaks as irregular formations. Yellowish nodes of varying size may also arise in the same region in a later phase. Maculae often originate in the centre and also more laterally in the cornea. Sensation in the cornea is frequently impaired.

Lattice dystrophy was described by Biber (1890), Haab (1899) and Dummer (1899). Opinions still differ about the etiology and other aspects of lattice dystrophy.

Vrabec (1957) demonstrated by silver staining an autopsy specimen that the dystrophic lattice corresponds to the hyaline degenerated nerves of the cornea. Wolter & Henderson (1963) came to the same conclusion. According to Vrabec primary dystrophic changes occurred in Schwann's sheath. He established dystrophic changes also in the corneal keratoblasts and in neurohistologic studies encountered changes even extraocularly: lesions in the nuclei of the VII, X and XII cerebral nerve pairs and dystrophy in the muscles innervated by these nerves. Hogan & Alvarado (1967) in their electron microscopic study were unable to demonstrate changes in the corneal nerves in the presence of lattice dystrophy. Amyloid or para amyloid has been observed as extracellular aggregations in the corneal parenchyma in many cases of lattice dystrophy (Seitelberger & Nemetz 1961, Klintworth 1967, Smith & Zimmerman 1968, Garner 1969, Winkelman & Delleman 1970, Winkelman, Delleman & Ansink

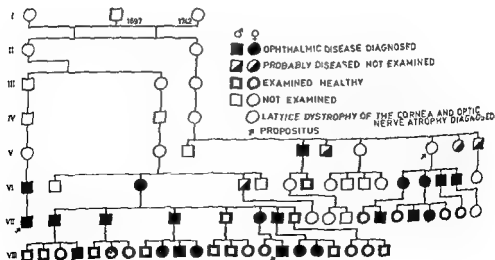


Fig. 1
Pedigree of an A1 family from Perno

Lattice Dystrophy of the Cornea

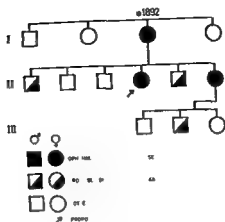


Fig 3

Pedigree of an A3 family from the Eura Eurajoki Kuusinen district



Fig 4a

Central in the bulbar conjunctiva five hours after the onset of the episode. The patient was a man 53 from group A1; Unstained biopsy specimen under polarisation in microscope ($\times 40$)

polarising microscope and after staining with the performic acid Alcian blue staining method of Adams & Sloper (1956) with a light microscope

Additional histologic specimens for the amyloid studies were fixed in formaldehyde and embedded in paraffin. The following staining methods were employed in the amyloid studies: Congo red (greenish birefringence in polarised light), haematoxylin-eosin, Van Gieson, PAS and crystal violet.

The medical examinations of the patients were performed in a medical outpatient department or in the ward (mainly Hivela Hospital).

Results and findings

Group A consisted of 25 patients examined by me. They belong to three families, all from south-west Finland. Family A1 was from Pernio, family A2 from the neighbouring parish of Kisko, and family A3 from the Eurajoki-Kuukainen district. The disease of group A has an autosomal dominant mode of inheritance. I have diagnosed the disease in three successive generations (Figs 1-3). Acute episodes of ophthalmic disease typical of group A usually begin at the age of 10-20 years. The youngest patient in whom I have seen an acute episode of the eye disease was 7 years old; the oldest was 86. An acute episode generally occurs in one eye at a time and may recur without known reason at intervals of a week or a couple of years. However, stress, tension, a cold, wind or bright dazzling light often seem to provoke an episode.

The ophthalmic symptoms of which the patients complain are a sensation of a mote in the eye, severe pain, lacrimal secretion and deterioration of vision.

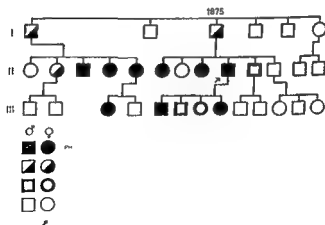


Fig. 2
Pedigree of an A2 family from Kisko



Fig 4c

The same unstained biopsy specimen under polarisation microscope as in Figs 4a and 4b ($\times 250$)

patients who have not had acute attacks for a long time. Pigment often accumulates on the posterior surface of the cornea. Sensation in the cornea is impaired little by little. It is usually already clearly weakened in patients aged 40. Vision does not deteriorate very much in general. It was 0.33 or poorer in only three patients over 50. Open angle glaucoma was diagnosed in one case when the patient was 82 years old.

The plasma cholesterol level of nine patients of group A was studied. It was fairly high (≥ 6.0 mmol/l) in five of them.

The results of the histologic examination for group A (Figs 4a, b, c and 5a, b, c) were the following. Biopsy specimens of the bulbar conjunctiva studied under the microscope five and 24 hours after the onset of an attack displayed abundant crystals in the region of the epithelial basement membrane and fewer in the epithelium and below the basement membrane. Some of the crystals were polarising—rectangular or fusiform; others were non-polarising and polygonal. Distinct dissolution of the crystals was seen 24 hours after the onset of the attack. They stained blue with Adams' and Sloper's performic acid Alcian blue technique. This positive reaction is suggestive of the presence of cystine or cysteine in the conjunctiva. No amyloid was seen in the conjunctival biopsy specimens.

Examination of the eye during an acute attack discloses heavy conjunctival and pericorneal congestion and tenderness when pressure is applied. Slit lamp examination reveals greyish yellow polygonal crystals in the anterior part of the corneal parenchyma roughly in its anterior third. The crystals are usually most numerous on the side where the congestion is most intense. They may form a dense cluster in a small area. The corneal epithelium usually is intact. Similar crystals can be seen in the aqueous and indeed are visualised best there. They may then take the form also of corneal precipitates.

Within a few hours, sometimes not until after a couple of days, the crystals lose their angularity and disappear from the aqueous. There remains at first a diffuse aqueous flare which disappears in 1 to 5 days. The crystals disappear from the cornea too, but some opacity and oedema remain for days or weeks, especially in the anterior part of the parenchyma. Vision is then 0.4-0.6. No posterior synechiae develop. The episodes become fewer and diminish in intensity with advancing age in some cases.

The cornea may be clear after the episodes, but in some eyes scars may remain in the anterior part of the corneal parenchyma. In a part of the patients - in nine in my own series - manifest lattice dystrophy with glassy streaks and sometimes yellowish nodes develops. The youngest patient with distinct incipient lattice dystrophy was 25 years old. The fibres of the dystrophic lattice sometimes shrink into thread like chalk white streaks in elderly



Fig. 4b

The same unstained biopsy specimen under polarisation microscope as in Fig. 4a ($\times 740$)

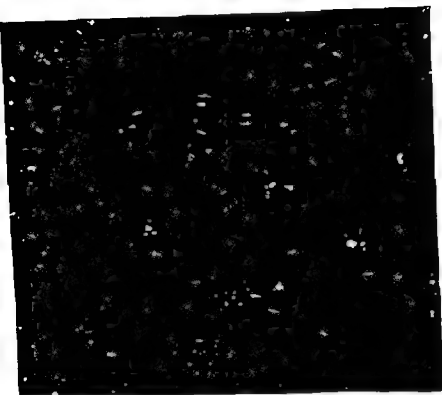


Fig 5b

The same unstained biopsy specimen under polarisation microscope as in Fig 5a ($\times 50$)

koski patient has not yet been investigated. All of the seven families in group B3 had forebearers in neighbouring villages (e.g. Lammi) in south-east Finland in an area of approx. 50×25 km but no common lineage has yet been established for them (Fig. 8).

The disease of group B has an autosomal dominant mode of inheritance (Figs 6 and 8).

The ophthalmic symptoms begin between the ages of 35 and 66 years. The eye disease of group B also appears as episodes which may occur a couple of times a year or at intervals of a few years. The symptoms usually are smarting, itching and blurring, generally in both eyes simultaneously. Vision may dim for some days or even longer (0.5-1.0). The ophthalmic symptoms often are so mild that lattice dystrophy of the cornea is diagnosed as a subsidiary finding.

Slit lamp examination during an attack usually reveals primarily small

Group B consisted of 22 patients who came from the eastern part of Uusima province western Kymi and south east Häme – that is from the same region as Meretoja's material. They all had very distinct lattice dystrophy of the cornea. The patients belonged to 18 families. There were two patients from each of four families: two sisters, two brothers, one father and son and one mother and daughter. In addition, the daughter of a male patient had indefinite lattice dystrophy and the daughter of a female patient had recurrent corneal erosions which are the phase that precedes lattice dystrophy. The patients are distributed into three groups according to their domicile. The forefathers of group B1 lived at the mouth of the River Kymi at the turn of the 17th century. One of the five families in the group is related to another two (Fig. 6). The family of two Kymi patients has not yet been investigated. It was recently discovered that one of the two belongs also to Meretoja's series. Five families of group B2 have a common lineage in present day Kuusankoski (Fig. 7). The family of the sixth Kuusan

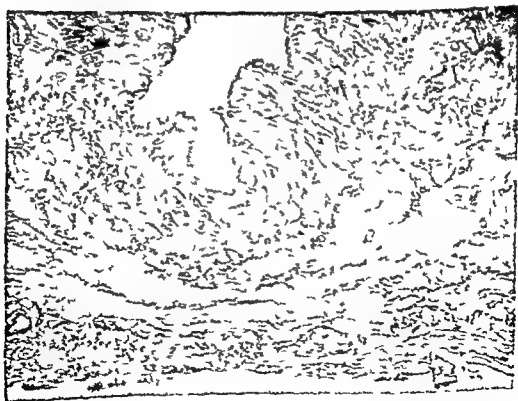


Fig. 5a

Crystals in the bulbar conjunctiva 24 hours after onset of the episode. The patient was a woman of 54 from group A. Unstained biopsy specimen under polarisation microscope ($\times 240$).

Lattice Dystrophy of the Cornea

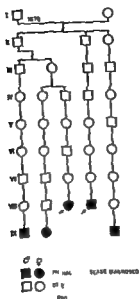


Fig 7

Common lineage of the families B2 The forefathers lived in Kuusankoski

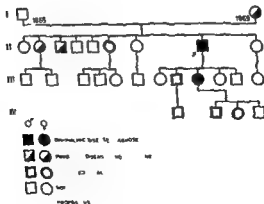


Fig 8

Pedree of one B3 family All seven B3 families had ancestors in an area 20 x 50 km in South east Hame



Fig 5c

The same unstained biopsy specimen under polarisation microscope as in Figs 5a and 5b ($\times 500$)

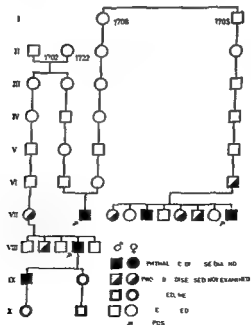


Fig 6

Pedigree of a BI family from Kyau district



Fig 10

Crystals in the bulbar conjunctiva 24 hours after the onset of the episode. The patient was a woman of 67 from group B3 with no amyloidosis. Unstained biopsy specimen under polarisation microscope ($\times 250$)

oldest patient aged 86 had in addition to corneal lattice and abundant yellowish nodes clearly discernible nodes also in the bulbar conjunctiva. Frequently pigment is seen on the posterior surface of the cornea in a later phase.

Glaucoma was diagnosed in five patients of group II. One of them has died. The other four have open angle glaucoma and their intraocular pressure rises during the presence of corneal erosions and especially of an ulcer. Two patients

epithelial erosions in the cornea they may be limited to a small round area in the centre of the cornea in youngish patients. They occur later irregularly throughout the cornea and especially in the lower part. Some pericorneal and conjunctival redness is seen also. The erosions may take from 10 days to nine months to heal. An ulcer was observed later in the centre of the corner of 11 patients. It recurred in some of them. There was a flare in the aqueous humour at the same time as the ulcer appeared. Crystal like formations were seen in the aqueous in three of these cases. During the erosions and ulceration pale grey sediment was seen on the boundary of the corneal epithelium and stroma and in the nerves and posterior surface of the cornea. Lattice dystrophy originates in the anterior part of the corneal parenchyma after months or years. There was one patient whose corneal ciliary nerves were of normal appearance in the limbic region during and even after the ulceration but elsewhere some were notably thickened pale grey and merely and others were glassy and clearly demarcated. A roundish scar often forms in the centre of the corner in a later phase of the disease it may thicken and even begin to project. The

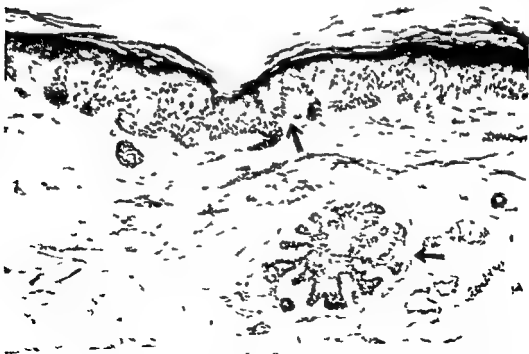


Fig 9

Amyloid in a biopsy specimen taken from the skin of the hand (arrows). Congo red staining ($\times 250$). The patient is a woman of 59 from group B3 and the same as in Figs 11 and 12.



Fig 10

Crystals in the bulbar conjunctiva 24 hours after the onset of the episode. The patient was a woman of 6, from group B3 with no amyloidosis. Unstained biopsy specimen under polarisation microscope ($\times 250$)

oldest patient aged 86 had in addition to corneal lattice and abundant yellowish nodes clearly discernible nodes also in the bulbar conjunctiva. Frequently pigment is seen on the posterior surface of the cornea in a later phase.

Glaucoma was diagnosed in five patients of group B. One of them has died. The other four have open angle glaucoma and their intraocular pressure rises during the presence of corneal erosions and especially of an ulcer. Two patients

patient in whom no amyloidosis had been established and from another patient who had amyloidosis 24 hours and seven days after the onset of symptoms respectively. In the epithelial basement membrane of both patients large groups of crystals similar to those in Group A were seen. There were fewer crystals in the epithelium and beneath the basement membrane (Figs 10 and 11). The crystals stained blue with the cystine technique of Adams & Sloper suggesting the presence of cystine or cysteine (Fig 12. The crystals are black in the picture). Fig 12 shows the same biopsy specimen as seen in Fig 11 unstained and the patient is the same as in Fig 9. Amyloid was found in biopsy specimens from the hand (see the picture), leg, rectal mucosa, lower palpebral conjunctiva and bulbar conjunctiva.

Discussion

The results suggest that the primary disease proper is a hereditary metabolic disorder in which cystine participates in both group A and group B. Lattice dystrophy of the cornea is a sequel of the disease. At least some of the ramifying streaks of the cornea that are characteristic of dystrophy are damaged ciliary nerves as is apparent from e.g. the case in which different stages of the disease were seen in the ciliary nerves.

The disease of group A in particular shows similarity with the disease group termed dysproteinemia by e.g. Duke Elder (1965) or paraproteinemia by Blobner (1938), Palm (1947), Burki & Rohner (1955), Burki (1958) and Aronson & Shaw (1959). Crystals originate in the cornea in them too.

Amyloidosis seems to be a secondary phenomenon in group B, the metabolic disorder which causes the crystals is probably of the same type in both groups but amyloidosis occurs only in group B. The crystal producing metabolic disturbance in group B also occurs earlier than does amyloidosis. Moreover both crystals and amyloid were established in the same biopsy specimen in the epithelial basement membrane of the bulbar conjunctiva of group B during an episode of the disease. Further evidence of the secondary character of amyloidosis is that it was present in only some of the cases of group B even in the same family, one brother with lattice dystrophy had amyloidosis and the other did not. Even as a secondary condition amyloidosis suggests that primary metabolic disorder is a systemic disease.

A conspicuously large proportion of group B patients especially had a fairly high plasma cholesterol level. According to the literature there may be disturbances of more than a single substance in anomalous metabolism.

Five of the 22 patients in group B and one of the 25 patients of group A had glaucoma. Although the question of a rising intraocular pressure during the crystal provoking episode of the disease requires further study it seems possible that the crystals in the aqueous humour for example may obstruct the flow of fluid in the eye and thus cause elevation of intraocular pressure.

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DYNAMIC TONOMETRY
V Further Studies of the Corneal Indentation Pulse
in Temporal Arteritis

BY

IVAR HØRVEN

Dynamic tonometry was performed in 22 patients with temporal arteritis. Ocular involvement was recognized by a statistically significant reduction of intraocular pressure and a marked and characteristic reduction of the corneal indentation pulse (CIP) amplitudes. Relative crest time evaluation of the CIP amplitudes demonstrated a typical increase characteristic for vascular obstruction. Evidence of impaired ocular blood supply was demonstrated also in eyes and patients with full vision, the diagnosis being later confirmed by a temporal artery biopsy.

Key words: central retinal artery embolism - corneal indentation pulse - crest time - dynamic tonometry - giant cell arteritis - intraocular pressure - temporal arteritis

The purpose of the present study is to draw attention to dynamic tonometry (Hørvén 1965) as an easy, accurate and safe clinical test in patients with temporal arteritis. This test is sensitive enough to give conclusive evidence of reduced ocular blood supply also in patients with no visual impairment (Hørvén 1966b).

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Material

The material consists of 22 patients 14 men and 8 women and includes all patients with a well established diagnosis of temporal arteritis examined by the author in the period 1967-1972. The men and women had an average age of 71.6 years (56-81) and 74.8 years (68-81) respectively. The patients were divided into three groups according to symptoms at the first examination.

Group 1 Patients with normal vision and fields in both eyes

This group consists of 5 patients (Cases 1-5) which were found by dynamic tonometry screening of roughly 50 patients with elevated erythrocyte sedimentation rate (SR) headache malaise polymyalgic rheumatism or proven temporal arteritis without visual loss. The diagnosis was confirmed by temporal artery biopsy in all cases. Two of the patients had episodes of diplopia prior to the first examination.

Group 2 Patients with functional loss in one eye

This group consists of 10 patients (Cases 6-15). Conclusive histological evidence of giant cell arteritis was found in all but one (Case 9) of these cases. The biopsy from Case 9 failed to show giant cells although definite pathological changes were demonstrated in the intima and media of the artery including partial disappearance of the internal elastic lamella.

Group 3 Patients with functional loss in both eyes

This group consists of seven patients (Cases 16-22). The diagnosis was confirmed by temporal artery biopsy in five of the patients. Biopsy was omitted in two typical cases Case 16 and Case 18.

Methods

Dynamic tonometry The dynamic tonometer (Horven 1965) is an improved standardized electronic Schiotz tonometer which records eye tension (>5 g plunger weight) and corneal indentation pulse (CIP) amplitudes at all tension levels. The dynamic tonometer output is 1 mV ($\pm 1\%$) per micron of plunger movement (Horven & Gjonnass 1972). An output of 50 mV therefore corresponds to 50 microns of plunger deflection i.e. one scale reading Schiotz. A recorder sensitivity of 20 mV per paper division and a paper speed of 1 mm per second were used for the eye tension recordings while a sensitivity of 2 mV

(or 1 mV) per paper division and paper speeds of 5 and 25 mm per second were used for the CIP amplitude registrations. Dynamic tonometry was performed repeatedly in all patients through a follow up period of from 1 week to 56 months.

The CIP amplitudes recorded by dynamic tonometry reflect the pulse synchronous alterations in intraocular pressure (IOP) which again are dependent upon the extra amount of blood which enters the eye in systole. If the ocular blood supply decreases a corresponding decrease is observed in the CIP amplitudes (Nornes et al 1971a).

Crest time This is defined as the time in seconds from base to summit of the pulse curve (Dillon & Hertzman 1941). For practical reasons the relative crest time was calculated (Fig 1) i.e. the crest time calculated as a percentage of one pulse cycle (Horven & Nornes 1971). This was done in 14 patients with 21 affected eyes. In patients with zero or small CIP amplitudes at the initial examination the relative crest time evaluation had to be postponed until treatment had initiated larger CIP amplitudes which would permit such calculations.

Definition of terms

Dynamic tonometry performed on 100 normal eyes gave an average CIP amplitude of 30.02 microns (SD = 10.048) (Horven 1970a). The lowest value recorded was 14 microns and the CIP amplitudes differed less than 15% between the two eyes of the same subject. In 10 subjects with 20 normal eyes and with an average age of 59.8 years (45-70) the CIP amplitude averaged 30.75

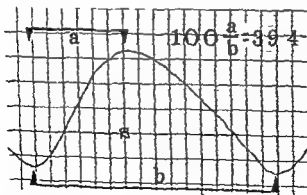


Fig 1

Relative crest time of the CIP amplitude is defined as the time from base to summit of the pulse curve calculated in per cent of the duration of one pulse cycle.

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The material consists of 22 patients 14 men and 8 women and includes all patients with a well established diagnosis of temporal arteritis examined by the author in the period 1967-1972. The men and women had an average age of 71.6 years (56-81) and 74.8 years (68-81) respectively. The patients were divided into three groups according to symptoms at the first examination.

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Definition of terms

Dynamic tonometry performed on 100 normal eyes gave an average CIP amplitude of 30.07 microns (SD = 10.048) (Hørvén 1970a). The lowest value recorded was 13 microns and the CIP amplitudes differed less than 15% between the two eyes of the same subject. In 10 subjects with 20 normal eyes and with an average age of 59.8 years (45-70) the CIP amplitude averaged 30.75

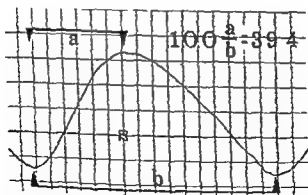


Fig. 1

Relative crest time of the CIP amplitude is defined as the time from base to summit of the pulse curve calculated in per cent of the duration of one pulse cycle.

microns ($SD = 10.351$) and the relative crest time averaged 41.5% (36.7–45.0 $SD = 2.34$) (Horven & Nornes 1971). This indicates that 99% of the normal population of this age group should yield a relative crest time of $41.5\% \pm 2.58 \cdot 2.34 = 41.5\% \pm 6.01\%$ between 35.5% and 47.5%. The IOP averaged 16.6 mmHg ($SD = 4.63$) in these 20 normal eyes (Friedenwald's 1955 converting table).

In accord with the above findings a pathological result of dynamic tonometry with reference to temporal arteritis may be defined as follows:

- 1 By demonstration of a repeated difference in CIP amplitudes between the two eyes of 15% or more
- 2 By recording CIP amplitudes of 12 microns or less in one or both eyes
- 3 By demonstration of a relative crest time above 47.5% in one or both eyes

Results

Ocular involvement. At the initial examination pathologically reduced CIP amplitudes were found in 35 eyes although only 23 of these had suffered visual impairment (Table 1). In addition one eye (Case 12) had visual loss with a CIP amplitude reduction of only 13% on the affected side. Most probably this

Table 1

Composition of material with positive dynamic tonometry test results obtained at the initial examination

	No. of patients	Visual loss	No. of patients with pathological test result		No. of eyes with pathological test results
			one eye	both eyes	
Group 1	5	none	9	2	7
Group 2	10	one eye	4 ²	5	14 ²
Group 3	7	both eyes	0	1	14
Total	22	24 eyes	14 ²	14	35 ²

² = Case 12 demonstrated a 13% decrease in CIP amplitudes 11 days after heavy steroid medication was started (see text)

may be explained by the fact that due to summer vacation the first dynamic tonometry examination was performed 11 days after heavy steroid medication was commenced. At this time the SR had dropped to 28 mm per hour from the initial value of 78.

During the follow up period a recurrence occurred in four patients after 6, 10, 19 and 47 months respectively. This was demonstrated by a CIP amplitude reduction and/or an increased SR. At the second attack two of the patients (Case 12 and Case 13) also suffered involvement of the other eye. Thus the present study demonstrated ocular involvement in 38 of the 44 eyes. Including the recurrences 14 of the 17 patients in Group 2 and Group 3 showed bilateral ocular involvement i.e. 82%.

Erythrocyte sedimentation rate The initial SR was elevated in all patients with an average of 87.9 mm per hour (40-140) (Table II). Routine therapy was administration of 120 mg prednisolone for two days followed by a step wise reduction in doses. A SR below 30 was usually obtained within 5-7 days. There after the steroid intake was adjusted to the lowest value which kept the SR below this borderline. In most patients a daily dose of 5-15 mg prednisolone was required for years. Some of the patients were adequately controlled with a dose of 10-30 mg prednisolone every other day.

Visual acuity Table III gives the initial visual acuity of the 36 affected eyes. A further visual impairment was seen in two patients during the first week of treatment (Case 14: finger counting (f.c.) 2 m - light perception (l.p.) 2 m; Case 21: 20/140 - f.c. 2 m). On the other hand in five eyes the vision improved during the first week of treatment (Case 6: right eye f.c. 1 m - 20/120; left eye l.p. 2 m - f.c. 2 m; Case 13: f.c. 1 m - 20/50; Case 16: f.c. 10 cm - f.c. 2 m; Case 22: f.c. 1 m - f.c. 5 m). After the first week of treatment no change in vision was ever recorded except for a temporary impairment in two of the four cases with relapses.

Dynamic tonometry A few examples may help visualize the information which was obtained by dynamic tonometry in these patients.

Case 13 (male, aged 66) had symptoms in the left eye of 4 days duration at the first examination. His right fundus appeared normal while the left demonstrated ischemic lesions. The visual acuity was 20/40 and f.c. 1 m and the CIP amplitudes measured 20 and 12 microns respectively in the right and left eye (fig. 2). Steroids had a fair effect on the SR but the CIP amplitudes continued to decrease on the left side. On the sixth day the visual acuity fell to 20/100 and an ischemic lesion was noted in the right fundus. Treatment was increased including rheomakrodex infusions and the visual acuity improved.

Table II

CIP amplitudes and SR results at the initial and final examinations

Case no	Sedimentation rate (mm per hour)		CIP amplitudes (microns)				Follow up period (months)
	initial	final	initial right	initial left	final right	final left	
1	115	30	8	12	15	17	1/2
2	110	—	10	10	21	18	4
3	94	16	14	9	24	20	5
4	125	37	36	8	38	27	8
5	77	21	14	9	16	16	23
6	48	11	9	9	—	—	1
7	60	56†	28	1	28	20	17
8	112	18	2	20	20	25	34
9	40	10	12	6	22	13	19
10	52	16	10	0	16	12	4 ^o
11	97	5	1	0	13	14	39
12	79	12	60	52††	59	54	50
13	98	17	20	12	20	24	56
14	40	18	12	29	9	21	41
15	78	6	9	10	9	8	6
16	50	20	10	4	30	24	32
17	140	25	9	5	26	16	1
18	105	28	9	12	14	14	1/2
19	91	14	4	6	—	—	1
20	81	—	0	0	—	—	(2 days)
21	92	4	8	8	40	26	24
22	95	21	2	2	24	24	40

† = Case 7 urinary tract infection

†† = Case 12 initial dynamic tonometry examination was performed 11 days after heavy steroid medication was commenced (see text)

to 20/40 on both eyes. Half a year later he suddenly suffered a new attack of his temporal arteritis with SR increase to 110 mm per hour, zero CIP amplitudes and a reduction of visual acuity to 20/50 in both eyes (Fig. 2). Treatment was once again increased and the vision improved to 20/40 and 20/30. After a follow up period of 56 months the CIP amplitudes measured 24 and 20 microns respectively in the right and left eye.

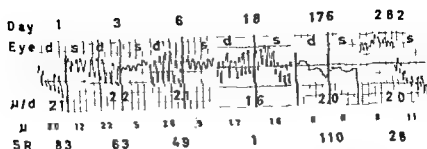


Fig 9

Dynamic tonometry results of Case 13 demonstrating a bilateral relapse 176 days after start of treatment d = right eye s = left eye μ/d = microns of plunger deflection per paper division

As mentioned a positive dynamic tonometry result was found in seven eyes of the five patients in Group 1 Case 3 (female aged 78) had symptoms compatible with polymyalgic rheumatism and an SR of 125 mm per hour The CIP amplitudes were reduced to 8 microns on the left eye (Fig 3) Steroid medication had a beneficial effect on the CIP amplitudes indicating that there was no longer any imminent danger of visual loss (Fig 3)

Case 11 (male aged 17) experienced moderately reduced vision of the right eye for one week when the eye suddenly became amaurotic The CIP amplitudes measured 1 micron on the right eye and zero on the left (Fig 4) although he had suffered no symptoms from the left eye The SR was 91 mm per hour and

Table III
Initial visual acuity of the 36 affected eyes

	0 0-40 700	fc 1 m-fc 5 m	lp or amaurosis
(r up)	7	0	0
(r up)	5	3	7
(roup 5	3	"	9
Total	15	3	10

Three patients (Cases 13-15) suffered bilateral amaurosis

Table II
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Case no	Sedimentation rate (mm per hour)		CIP amplitudes (microns)				Follow up period (months)
	initial	final	initial right	initial left	final right	final left	
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2	110	—	10	10	21	18	4
3	94	16	14	9	24	20	5
4	125	37	16	8	35	27	9
5	77	21	14	9	16	16	23
6	48	11	8	8	—	—	1
7	60	56†	28	7	25	20	1/2
8	112	18	2	20	20	25	34
9	40	10	12	6	22	18	19
10	52	16	10	0	16	12	4 ^a
11	97	5	1	0	13	14	39
12	18	12	60	52††	58	54	50
13	83	17	20	12	20	24	56
14	40	18	12	29	8	21	41
15	78	6	9	10	8	8	6
16	50	20	10	4	30	24	37
17	140	25	9	5	26	16	1
18	105	25	9	12	14	14	1/2
19	91	14	4	6	—	—	1
20	81	—	0	0	—	—	(2 days)
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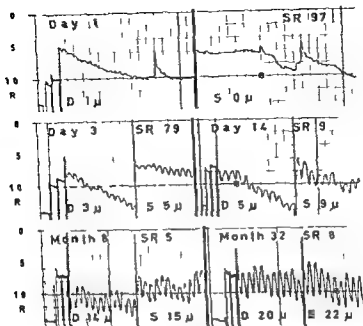


Fig 4

Case 11 had amaurosis on the right eye (D) and normal vision on the left (S) although extreme CIP amplitude reductions were demonstrated on both eyes. The CIP amplitudes were favorably influenced by treatment. R = scale reading Schiotz Sensitivity settings 70 and 7 mV per paper division.

period of muscular pain without headache she suffered a sudden loss of vision to 1p on the left eye. The SR was 52 mm per hour and the CIP amplitudes measured 10 and zero microns respectively. No visual loss occurred in the right eye.

Crest time

In a few patients the relative crest time evaluation was performed late in the follow up period with normal values as a result. In other patients the evaluation was performed earlier in the follow up period or at the first examination. As a rule a marked increase in relative crest time was found in these eyes. The 21 eyes demonstrated an average CIP amplitude of 14.9 microns (4-36) with a relative crest time average of 48.4% (40.5-53.9 SD = 4.06). Compared with the 10 normal eyes average of 41.5% this is a highly significant increase.

routine medication was started. The next day an ischemic spot was observed close to the left optic disc; the vision of the left eye was, however, not involved. The right eye remained amaurotic. The increment in CIP amplitudes observed during treatment (Fig. 4) indicates that recanalization occurs in the affected arteries with increased ocular blood supply as a result.

Differential diagnosis versus central retinal artery (CRA) embolism

CRA embolism sometimes mimics temporal arteritis. By using dynamic tonometry it is easy to distinguish between these two disorders as shown in Fig. 5. Curve A is from a 52-year-old man. He suffered an abrupt visual loss to 1p on the right eye; the SR was 73 mm per hour. CIP amplitudes of 24 microns were recorded on both eyes, which ruled out temporal arteritis as a diagnostic possibility. A chest X-ray revealed an infiltrate in the right lung which explained the SR elevation. Curve B is from Case 10 (female, aged 68). After a

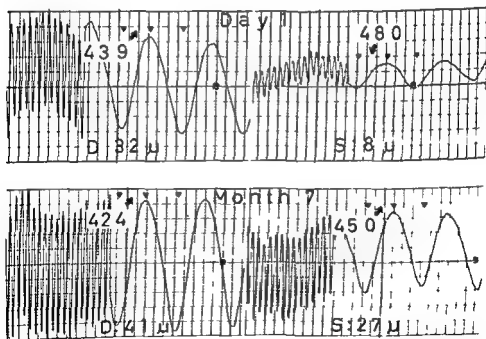


Fig. 3

Case 3 had normal vision on both eyes. Impairment of the blood supply to the left (S) eye was demonstrated by CIP amplitude reduction and relative crest time increment (above). The pathological findings were favorably influenced by treatment (below). R = scale reading Schiotz. Sensitivity setting: 1 mV per paper division.

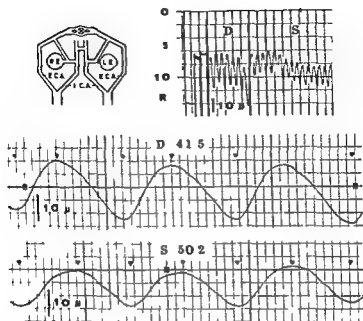


Fig 6

Increased relative crest time value caused by giant cell arteritis obstruction of the ocular blood supply in Case 10 left eye R = scale reading Schiotz

Discussion

Most reports of temporal arteritis have not included the IOP. Wolter & Phillips (1965) reported a typical case of neovascular glaucoma which developed as a secondary complication in an amaurotic eye as a result of giant cell arteritis. Case 14 of the present study had a borderline IOP of 24.6 mmHg on the affected side. As demonstrated however the typical IOP alteration in temporal arteritis is a decrease which is more pronounced by complete and abrupt impairment of the ocular blood supply. This is in accordance with what has previously been found for impaired ocular blood supply by carotid artery obstruction (Binke 1966; Nornes et al 1971a, b).

It is well known that digital plethysmogram pulse changes occur in arterial occlusive disease (Matoba 1934). These pulse wave changes include a delayed peak and rounded contour (Lund 1956; Conrad & Green 1964) with an increased crest time (Dillon & Hertzman 1941). A reduction of CIP amplitudes initiated

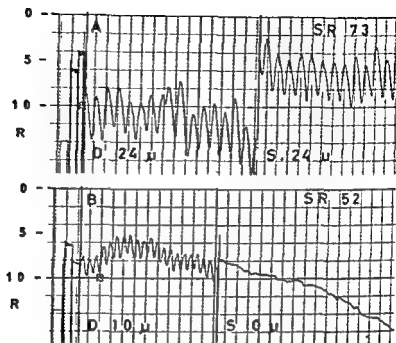


Fig 5

Typical dynamic tonometry results obtained from patients with central retinal artery embolism (A) and temporal arteritis (B) R = scale reading Schiotz Sensitivity settings 20 and 2 mV per paper division

(Student's t test $t = 6.47$ $P < 0.001$) Of these 21 eyes 15 showed relative crest time values above the upper normal limit of 47.5%. Case 10 is presented in Fig 6 and Fig 3 demonstrates how the relative crest time value is favorably influenced by treatment

Intraocular pressure

With few exceptions the IOP was lowest in the affected or most affected eye. And more so if there had been a sudden and complete loss of vision. This is shown in Figs 4 and 5. Eight of the affected eyes (i.e. 22%) showed IOP values below 10 mmHg at the initial examination; the lowest value recorded was 6.2 mmHg. One eye (Case 14) had an initial IOP of 24.6 mmHg. The IOP averaged 12.3 mmHg (SD = 3.65) in the 36 affected eyes, which is a statistically highly significant decrease compared with the 20 normal eyes average of 16.6 mmHg (Student's t test $t = 3.54$ $P < 0.001$).

sia. A similar case was observed recently in Oslo City Hospital (Bergaust 1968). Most probably these eyes which yielded no symptoms prior to general anesthesia still had a reduced ocular blood supply as a consequence of giant cell arteritis lesions in their ophthalmic arteries. The above observations may be explained by the fact that a marked decrease in CIP amplitudes is also initiated by ether or Halothane general anesthesia (Hørvén & Syrdalen 1970). When this anesthesia effect comes in addition to the reduction in ocular blood supply induced by the giant cell arteritis, a further decrease in CIP amplitudes and ocular blood supply may be initiated with amaurosis as a result. As a consequence of this interpretation it is advisable for patients suffering from temporal arteritis to have a dynamic tonometry test performed prior to accepting surgery under general anesthesia. If this test demonstrates a decrease in CIP amplitudes in eyes with useful vision, the general anaesthesia should if possible be postponed.

Acknowledgment

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by impairment of ocular blood supply was first demonstrated clinically by carotid artery obstruction (Castrén & Lavikainen 1964) and later confirmed by simultaneous recording of CIP amplitudes and internal carotid artery blood flow during mechanical clamping of this artery (Nornes et al 1971a). An increase in relative crest time of the CIP amplitudes has also been observed by carotid artery obstruction (Horven & Nornes 1971). The present findings therefore, point to a severe reduction in ocular blood supply affecting not only the retina but the choroid as well. The retinal vessels constitute only a small fraction of the total intraocular vascular bed. In accordance with this only a minor and negligible decrease has been found in the intraocular pulsations by CRA embolism (Thiel 1928, Suzuki 1962). All 10 cases with CRA embolism examined by the author gave CIP amplitudes within the normal range. CRA embolism is therefore easily ruled out as a differential diagnostic possibility by the use of dynamic tonometry, while carotid artery obstruction may yield results similar to what is seen in temporal arteritis (Horven et al 1971, Nornes et al 1971b) although the CIP amplitude reduction as a rule is less pronounced.

Dynamic tonometry is superior to other diagnostic methods for temporal arteritis because of its ability to demonstrate impairment of ocular blood supply also in patients with no loss of vision. Together with SR examinations it is also a valuable guide through the entire follow up period which should be long. Recurrences of ocular complications have been reported after 3 (Miller 1964) and 7 (Cullen 1972) years of treatment. In the present study exacerbation was seen in four cases after 6, 10, 19 and 47 months respectively. At these times the maintenance dose of prednisolone suddenly became inadequate. The exacerbations were however, controlled without further loss of vision by a temporary increment in steroid intake. In order to minimize the risk of recurrences it is probably wise to give a maintenance dose high enough to provide SR results below 30 mm per hour which may be obtained in the vast majority of cases.

If the patient has suffered symptoms for only a short time and the visual loss is incomplete, heavy steroid medication may initiate visual improvement in some of the affected eyes. If so, the visual improvement occurs during the first week of treatment, after this time the visual loss seems permanent. This finding agrees with other reports (Cohen 1972).

A dynamic tonometer is not a prerequisite for CIP amplitude registrations. Electronic tonometers of other designs may be used as well, provided they give a linear output, are connected to a recorder which offers suitable sensitivity settings, and either tonometer or recorder are equipped with a zero suppression unit.

McGowan (1967) reports a case of temporal arteritis which was amaurotic in one eye and developed amaurosis in the other eye following general anesthetic

512. A similar case was observed recently in Oslo City Hospital (Bergaust 1968). Most probably these eyes which yielded no symptoms prior to general anesthesia still had a reduced ocular blood supply as a consequence of giant cell arteritis lesions in their ophthalmic arteries. The above observations may be explained by the fact that a marked decrease in CIP amplitudes is also initiated by ether or Halothane general anesthesia (Hørvén & Syrdalen 1970). When this anesthesia effect comes in addition to the reduction in ocular blood supply induced by the giant cell arteritis a further decrease in CIP amplitudes and ocular blood supply may be initiated with amaurosis as a result. As a consequence of this interpretation it is advisable for patients suffering from temporal arteritis to have a dynamic tonometry test performed prior to accepting surgery under general anesthesia. If this test demonstrates a decrease in CIP amplitudes in eyes with useful vision the general anaesthesia should if possible be postponed.

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MELANIN AFFINITY OF A NEW
ANTITUBERCULOUS DRUG RIFAMPICIN INVESTIGATED
BY WHOLE BODY AUTORADIOGRAPHY

BY

GUNNAR BOMAN

Key words: rifampicin - melanin - uveal tract - retina pigment epithelium

Melanin affinity has for some years been discussed in relation to the pathogenesis of drug induced eye diseases especially chorioretinopathy caused by phenothiazines and chloroquine (Potts 1962)

While studying the distribution of rifampicin a new very effective anti-tuberculous drug I have found evidence of a possible affinity to melanin. Male mice weighing 20-25 g and female mice in late pregnancy both of the albino NMH strain and the brown CBA strain were used. ^{14}C labelled rifampicin (1 mg / g C) was injected i.v. The mice were sacrificed after different time intervals of from 5 min to 4 days. The whole body autoradiography technique of Ullberg (1954, 1958) was used. Immediately after sacrifice the animals were deep frozen. Sagittal sections (20-60 μ thick) were cut, fixed to tape, apposed to roentgen film and exposed for periods of up to one year. Before development sections and film were separated. The detailed results will be published elsewhere, only the difference in distribution between albino and pigmented

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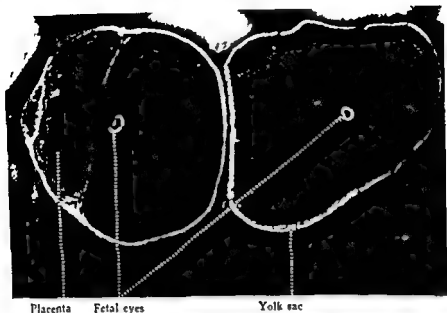


Fig 9

Detail of an autoradiogram of a pregnant pigmented mouse showing two fetuses 4 hours after an iv injection of ^{14}C rifampicin. Note high uptake in the fetal eyes and the yolk sac

bw) for $1\frac{1}{2}$ -2 years indicating that possibilities for ocular side effects may exist. However, since 1966 when the first clinical trials started more than 10 000 tuberculous patients have undergone long term treatment with rifampicin and so far no proven eye damage has been reported to the manufacturer (Cruppu Lepetit personal communication). Thus no reason for clinical alarm seems to exist.

On the basis of these findings Knave et al (1973) have studied the ERG response in sheep after iv injection of rifampicin and have found a selective effect on the c wave considered to reflect the pigment epithelial cell activity. Further investigations to assess the clinical importance of these observations are in progress.

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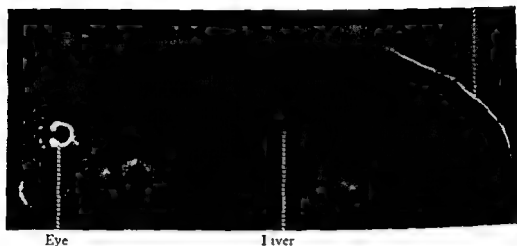


Fig 1

Autoradiogram of a pigmented mouse 4 days after an i.v. injection of ^{14}C rifampicin. Note high radioactivity (white) in the uveal tract and the skin.

mice is presented here. In albino mice only faint radioactivity was visible in the eye during the first 24 hours. In contrast there was a marked radioactivity in the uveal tract (and presumably in the retinal pigment epithelium) and the skin of pigmented mice especially from 4 hours after the injections. Four days after the injection radioactivity could be observed only in these parts of the eye, the skin and of course the liver which is the main excretory organ for rifampicin (Fig 1). In pregnant pigmented mice it was observed that the radioactivity passed the placenta and concentrated in the fetal eyes (Fig 2). High radioactivity was seen also in the eyes and the skin of 1 day old mice born 9 days after ^{14}C rifampicin had been injected in the mother.

In my opinion this difference in the distribution pattern of ^{14}C rifampicin between albino and pigmented mice may well be attributed to melanin affinity. In the eye high radioactivity was seen only in the uvea of pigmented mice. The resolution of the technique used does not differentiate uptake in the choroid from the retinal pigment epithelium. It remains to be demonstrated whether the radioactivity is due mainly to unchanged rifampicin or to radioactive metabolites.

Similar distribution patterns for chlorpromazine and chloroquine have recently been reported by Lindquist & Ullberg (1972) using the same technique. The frequency of ocular side effects during treatment with these drugs has been related to the total dose and the duration of therapy. In standard regimens for tuberculosis treatment rifampicin is given in a daily dose of 600 mg (10 mg/kg

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SELECTIVE EFFECT OF A NEW ANTITUBERCULOUS DRUG RIFAMPICIN ON THE π WAVE OF THE SHEEP ELECTRORETINOGRAM

BY

BENGT KNAVE HANS E PERSSON BERIT CALISSENDORFF
and SVEN ERIK G NILSSON

Key words: rifampicin - antituberculous drug - sheep - electroretinography - retinal - pigment epithelium

Quite recently it was found that i.v. injections of ^{14}C labelled rifampicin gave rise to marked radioactivity in the uveal tract (and presumably in the pigment epithelium) of the pigmented mouse (Boman 1973). This finding contrasted to the faint radioactivity obtained in the albino mouse. The difference in distribution pattern of ^{14}C labelled rifampicin between pigmented and albino mice was interpreted as being due to an affinity to melanin in the uvea and the pigment epithelial cells of the pigmented mouse retina.

Recently an ERG method was developed which allowed studies of the slow components of the sheep ERG (Knave, Møller & Persson 1972). One of these slow components is the π wave which is known to reflect the activity of the pigment epithelial cells in vertebrate retinas (Noell 1953, Brown & Wiesel

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1961 Steinberg Schmidt & Brown 1970) Furthermore it has been shown in electron microscopic studies that pigment epithelial cells of the sheep retina except those within the tapetal area contain melanin granules (Leure DuPree 1968 Nilsson Knave Persson & Lunt 1973)

Against this background we considered it pertinent to apply the above mentioned ERG technique to functional studies of the effects of rifampicin The present communication reports the effects on the dark adapted ERG after iv administration of single doses of rifampicin

Figs 1A and B show ERGs of the dark adapted sheep eye in response to a one sec-light stimulus with an intensity 4.0 log units above the *b* wave threshold The *a*-wave followed by the *b* wave are seen immediately after onset of stimulus More than half a second after cessation of light the slow *c* wave reaches its peak amplitude

In Fig 2 the ERG amplitudes of the dark adapted eye have been plotted for a time period of 280 min (upper trace *b* wave middle trace *c*-wave lower trace *a* wave) After 104 min (arrows) and 168 min (arrows) 20 and 40 mg/kg bw rifampicin respectively were injected intravenously Before the first injection the *a*- and *b*-wave amplitudes were found to be more or less constant whereas that of the *c* wave oscillated with a frequency of about 2/hour As can be seen in the diagram these oscillations seem to be superimposed upon a much slower oscillation (frequency of about 0.5/hour)



Fig 1

The ERG of the dark adapted sheep eye recorded 30 min before (A) and 10 min after (B) iv injection of 20 mg/kg bw rifampicin Amplitude calibration 250 μ V Time calibration 0.5 sec

Rifampicin Effect on Sheep ERG

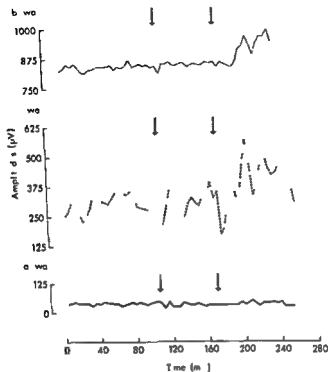


Fig 2

Effects of rifampicin on the *a* (solid line) *b* (dotted line) and *c* wave (broken line) of the dark adapted sheep ERG. After 104 min (arrows) and 168 min (arrows) 20 and 40 mg/kg b w rifampicin respectively were injected intravenously

After the injections of rifampicin the faster of these *a* wave oscillations increased in amplitude but did not change in frequency. A dose response effect was noted: the larger dose (40 mg/kg b w) resulted in large oscillations varying in amplitude from about 200 to about 550 μV . No effects were recorded in the *a* wave and the *b* wave amplitude did not change until about 25 min after the second large dose. At this moment the *b* wave amplitude increased and the observations at the end of the experiment indicated amplitude oscillations similar to those of the *c* wave.

Thus single i.v. injections of 20–40 mg/kg b w rifampicin result in selective effects on pigment epithelial cell activity as judged by the selective effects on the *c* wave of the sheep ERG. In this way the present report may serve as a functional confirmation of the melanin affinity of rifampicin suggested by

Boman (1973) in an autoradiographic study. Furthermore the present results point to the necessity of studies on the long term effects of the drug especially since standard treatment implies a daily dose of 600 mg (10 mg/kg b.w.) for 1.5–2 years. A new method for d.c. registration of the human ERG has been developed by Knave & Nilsson (1973). It seems that this method will be of value in clinical work for the detection of early side effects on the pigment epithelium (prior to damage to the neuroretina) of certain drugs i.e. rifampicin, chloroquine and chlorpromazine.

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*My eyes grow dim and my ears ring
Sappho*

SCOTOMA DUE TO ARTERIAL HYPOTENSION

BY

K. A. EKBOM

Auto observations of a characteristic scotoma due to arterial hypotension are reported. As far as I know, this has not been described in detail before. A small spot appears before each eye, temporal to and near the fixation point. These spots increase in size and unite to form an oval in the central part of the visual field. The oval has an extension of 10° vertically and 17° horizontally. It is a positive scotoma which wholly or partially covers the background. Peripheral to the oval, the visual field is intact. The scotoma fades and disappears while retaining its size and shape. The duration is a few minutes. The scotoma is probably caused by retinal ischemia. It is not identical, however, with the experimental blackout provoked by means of a cervical pressure cuff, an aviation centrifuge or ophthalmodynamometry.

Key words: scotoma - arterial hypotension - fainting - syncope

As is well known, fainting (syncope) is often preceded by visual disturbances. Usually, these are described in only a few words. The monograph on fainting by Engel (1962) contains, for instance, only the expression "blurring of vision".

I have interviewed 30 patients, nurses and students who have fainted one or more times. Some were unable to remember whether fainting had been preceded by any visual symptoms. Most of them said that vision had become clouded, grey or black. A physician said that he lost colour vision. None was able to give further details.

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I for several years I have regularly taken guanethidine (Ismelin®) for arterial hypertension. I have had ample experience of the side effects which are caused by low blood pressure when in a standing position. Among them is a characteristic scotoma which as far as I know has not been described before.

Scotoma

The scotoma starts with two small spots, one before each eye. The spots are situated temporal to slightly above and near the fixation point. When seen at arm's length (48 cm) they are about the size of a finger joint; at reading distance (30 cm) they measure approximately 15×15 mm.

When I try to fixate on one of the spots it moves upwards. Both spots grow slowly and then unite to form an oval with its longitudinal axis horizontal. The oval persists for one or two minutes and then fades and disappears. It is always the same size. It covers the whole of the palm and the greater part of the fingers (about 9×14 cm) at arm's length. On a wall at a distance of 370 cm the horizontal diameter is 95 cm and the vertical 55 cm. Thus the scotoma has an extension of approximately 10° by 17° . The visual field peripheral to the oval is always intact. In what follows the expression "spots" indicate the incipient scotoma and "oval" the fully developed scotoma.

Both the spots and the oval have the character of a positive scotoma. They resemble a mist or a cloud. Generally they are transparent and the background is seen more or less clearly. At times however the scotoma covers the background entirely. I may then be unable for example to recognize a face. When my eyes are open the scotoma is grey or pale green or slightly shimmering. It is not black. When my eyes are shut it is slightly luminous against a dark background. It looks about the same as when one has looked into a lamp and been dazzled. There are no scintillations. The oval does not decrease in size but fades away. The exact moment of its disappearance is difficult to decide. If I look at a grey wall or shut my eyes the scotoma may not be visible. But if I then look at the white ceiling it is still there though faint. I have occasionally timed it with a stopwatch. Once it took 1 min 41 sec for the scotoma to reach its maximum extension and on another occasion 3 min 24 sec from onset to its total disappearance. There have been no substantial divergences from these figures.

Thus the oval is formed by two spots in the vicinity of the fixation point which increase in size and become confluent. The right spot belongs to the right eye and the left spot to the left eye. If I shut my left eye and look at the

Scotoma and Arterial Hypotension

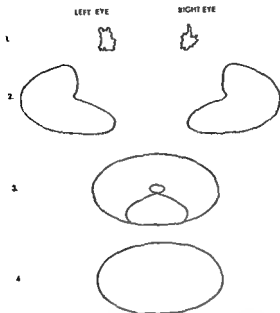


Fig 1

Schematic drawing of a hypotensive scotoma

1 Two small irregular spots appear immediately above and temporal to the fixation point which is denoted by a cross. The right spot belongs to the right eye and vice versa.

2 These spots have increased to their maximal size and extend also to the lower nasal quadrant of the visual field. Each spot is part of an oval.

3 In the center of the oval there is a quickly disappearing small area where vision is retained. In the lower part of the oval distinct contours show overlapping of the nasal parts of the two spots.

4 The final stage is an oval which always has the same shape and size (10 by 17°). The small area with retained vision and the contours due to overlapping have disappeared. The oval fades and disappears without changing its shape and size.

well. I see only the right spot and vice versa. With both eyes closed or open both spots are visible. The spots are not circular and their contours are irregular. The shape can vary. When first seen the spot is located only in the upper temporal quadrant of the visual field. When it grows it extends to the lower temporal quadrant and finally also to the lower nasal quadrant. This results in an overlapping of the two spots. Then I clearly see the lower right (nasal) contour of the left spot in the right lower quadrant of the oval and vice versa. I have never seen overlapping in the upper quadrants. Immediately after

Table I
Comparison between the scintillating and hypotensive scotomas

	<i>Scintillating scotoma</i>	<i>Hypotensive scotoma</i>
Character of scotoma	Negative	Positive
Colour	None	Greyish or greenish slightly luminous
Initial size at reading distance (30 cm)	Fragment of a letter in a book (approximately 1 mm)	Approximately 1 cm
Development	A crescent slowly growing in size and drifting towards the periphery of the visual field	Two spots increasing in size and becoming confluent then forming an oval in the central part of the visual field
Scintillations	Appear a few minutes after onset of scotoma	None
Defect in the visual field	Homonymously hemianoptic	Initial stage bitemporally hemianoptic. Later stage extending also into the nasal lower part of the visual field (overlapping)
Duration	11-34 minutes	A few minutes
Disappearance of scotoma	Moves out of the visual field	Fades away

the two spots have formed the oval there is often in its center a small oval area including the fixation point where vision is entirely retained. When I sit and look down at the floor from a distance of 1 meter this island is approximately 2×3 cm (1×1.5) with the longest axis horizontal. It rapidly diminishes in size and disappears within a few seconds. The fully developed oval is visible when both eyes are open and when one or both eyes are shut. Its outlines are slightly uneven. I have seen the oval hundreds of times. It has invariably been the same size and had the same appearance.

If I lie down or sit down the spots may disappear before they have reached their full size and have combined to form the oval. On one occasion the scotoma disappeared after 2 min 6 sec. Another time it lasted 1 min and 45 sec. On these

occasions it had not reached its maximal size. The spots usually are symmetric but there are exceptions. Once I saw a spot on the left side. It disappeared after 1 min 30 sec. No spot appeared on the right side. On another occasion a spot appeared on the left side. After 5 to 10 sec a smaller spot was seen on the right side. It increased in size and became confluent with the spot on the left side. The oval, however, did not have time to become fully developed on the right side before it faded and disappeared. On a single occasion two small spots were visible on the right side. They flowed together and formed a larger spot. Consequently for a short time there were three spots: one on the left side and two on the right.

It is easy to distinguish a scotoma due to hypotension from a scintillating scotoma (Table I). The Table is based on auto observations of 17 scintillating scotomas (to be published) and hundreds of hypotensive scotomas.

BLOOD PRESSURE AND SCOTOMA

For several years I have been treated for arterial hypertension with hydrochlorothiazide (Esidrex [®]) 12.5 mg per day and guanethidine (Ismelin [®]) in a dose that has varied between 10 and 35 mg per day and averaged about 10–20 mg per day. During treatment the blood pressure has been almost normal in a recumbent position. When I have been standing the pressure has been considerably lower. On several occasions it has been 80/60 mm without causing any subjective discomfort. My eyegrounds show retinal changes of grade I–II according to Keith et al. (1939). Otherwise examination of my eyes has given normal results except for slight hyperopia (2 diopters) and astigmatism. I have no doubt that my scotoma is connected with low blood pressure. It occurs most frequently immediately after I get up in the morning, never when I am in a recumbent position. It has a clear relation with other hypotensive symptoms which do not come within the scope of this paper. For example it appears when I go uphill, especially on a warm summer day. Because of the timing I have had no opportunity to have my blood pressure or my eyegrounds examined while a scotoma was in progress. The scotoma has occurred only during medication with guanethidine. On three occasions I have been without this medicine for just over a month. All hypotensive symptoms, including the scotoma, disappeared. The blood pressure rose gradually and I returned to guanethidine. The blood pressure then soon decreased and the scotoma appeared again. I have never fainted on account of hypotension because each time I have lain down or sat down. The scotoma and the other hypotensive symptoms then invariably disappeared.

Table 1
Comparison between the scintillating and hypotensive scotomas

	<i>Scintillating scotoma</i>	<i>Hypotensive scotoma</i>
Character of scotoma	Negative	Positive
Colour	None	Greyish or greenish slightly luminous
Initial size at reading distance (30 cm)	Fragment of a letter in a book (approximately 1 mm)	Approximately 1 cm ²
Development	A crescent slowly growing in size and drifting towards the periphery of the visual field	Two spots increasing in size and becoming confluent then forming an oval in the central part of the visual field
Scintillations	Appear a few minutes after onset of scotoma	None
Defect in the visual field	Homonymously hemianoptic	Initial stage bitemporally hemianoptic. Later stage extending also into the nasal lower part of the visual field (overlapping)
Duration	17-34 minutes	A few minutes
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the two spots have formed the oval there is often in its center a small oval area including the fixation point where vision is entirely retained. When I sit and look down at the floor from a distance of 1 meter this island is approximately 2 x 3 cm (1 x 1.5) with the longest axis horizontal. It rapidly diminishes in size and disappears within a few seconds. The fully developed oval is visible when both eyes are open and when one or both eyes are shut. Its outlines are slightly uneven. I have seen the oval hundreds of times. It has invariably been the same size and had the same appearance.

If I lie down or sit down the spots may disappear before they have reached their full size and have combined to form the oval. On one occasion the scotoma disappeared after 2 min 6 sec. Another time it lasted 1 min and 45 sec. On these

after a few seconds. During blackout the arterioles ceased their pulsations and resembled empty fine polyethylene tubing.

A simple method to provoke blackness due to ischemia in the retina is to press a finger against one eye while closing the other. Seven physicians and medical students performed this experiment. Blackness started after 4 to 7 seconds. After 10 to 16 seconds the whole visual field was black. The last remnant of vision was a small central island. Six subjects noted darkness first in the nasal part of the visual field. One was not able to tell where it started. Vision returned immediately when the finger was removed. I have also performed this experiment on myself several times and seen the central island of retained vision soon followed by complete blackness. I am not sure, however, where blackness begins. I could not in this way provoke the scotoma I have described in this paper, nor could the other subjects.

Arterial emboli are a common cause of retinal ischemia.

A 40 year old man with hypertension (210/100 mm) during the last two months once or twice a week had had attacks of blindness in his right eye. All attacks were identical. At onset there was blurring of vision. The first time he thought that his glasses were moist. He wiped them but his sight was not improved. Then there was complete blindness in the right eye starting on the nasal side. The last area with retained vision was located at the temporal border of the right visual field. Vision returned in the opposite direction. First a small part of the temporal field reappeared. Then normal vision rapidly spread in the nasal direction. He had taken the time with a stopwatch. Each attack lasted twenty minutes. He had not measured the time from onset to complete blindness but estimated it to be a few seconds. He used the word "blackness" but when I questioned him closer he said that the colour was perhaps more grey than black. On one occasion we had the opportunity to examine his eyegrounds during an attack. The arteries were empty and did not pulsate. The veins were wide and dark red. The diagnosis was transitory ischemic attacks. Angiography showed thrombosis in the right carotid artery. At operation an arteriosclerotic plaque with a fresh thrombosis in the internal carotid artery near the bifurcation was removed.

Walsh & Hoyt (1969) in their handbook on neuro ophthalmology write about fainting: "Central vision becomes blurred, the periphery of the field contracts, it is difficult to focus. Next vision blacks out. In many patients these cerebral events progress so rapidly that an accurate history regarding them is impossible to obtain. Possibly the vascular insufficiency in the temporal lobes obliterates memory for the event."

The difficulty of obtaining an accurate history agrees with my experience. For this reason I suppose that Walsh's description, at least in part, is based on the observations made during experimentally provoked blackout.

My own observations differ from the visual disturbances provoked by a cervical cuff, centrifugation, ophthalmodynamometry pressure with the finger on

Discussion

As far as I know the scotoma observed by me has not been described in detail before. In the literature on fainting I have found only very short descriptions. Usually one of the following words is used: blurred vision, blindness, dimness, greying, blackness, blackout. Two of the best descriptions have been made by a physician but not in a medical journal. The following quotations are taken from novels by Conan Doyle:

In *The Empty House* Sherlock Holmes' dramatic return had the following effect on Dr. Watson, who believed that his friend was dead: "I rose to my feet, stared at him for some seconds in utter amazement, and then it appears that I must have fainted for the first and last time in my life. Suddenly a grey mist swirled before my eyes, and when it cleared I found my collar ends undone and the tingling after taste of brandy upon my lips."

In *The Lost World* the young journalist narrowly escaped from being strangled by an ape man. "A thin oval tinted mist formed before my eyes and little silvery bells tinkled in my ears. Then he lost consciousness, but of course he was rescued in the very last second. This quotation is of special interest. In no other account of fainting I have seen the word 'oval'."

Duane (1967) in a broad review of the literature on experimental blackout and the visual system has defined "blackout" in the following way: "A person sees blackness but he is not unconscious". Greyout remains that nebulous state wherein there are contracted visual fields and possibly diminishing colour vision. Blackout refers to the total loss of vision."

Blackout has been studied experimentally in different ways. Rossen et al. (1943) induced cerebral anoxia in healthy young men by means of a cervical pressure cuff. Consciousness was lost in less than ten seconds. Before this the subjects experienced rapid narrowing of the field of vision, blurring of vision, with the field of vision becoming grey, and finally complete loss of vision. Jaeger et al. (1964) found that both in ophthalmodynamometry and during positive acceleration in a large aviation centrifuge the blackness started in the nasal field. "The defect approached hemianoptic character before marked temporal field loss began. The last remaining visual field was not at fixation but confined to an island located temporally between fixation and the blind spot." (In the paper on positive acceleration there seems to be some mistake for the pictures of the visual field are not in accord with the conclusions quoted above. In Duane's review of this paper (1967) the same conclusions are repeated but there are no pictures.)

Blackness appeared probably after a very short time because in an earlier paper by Duane (1954) on experiments with the centrifuge blackout occurred

after a few seconds. During blackout the arterioles ceased their pulsations and resembled empty fine polyethylene tubing.

A simple method to provoke blackness due to ischemia in the retina is to press a finger against one eye while closing the other. Seven physicians and medical students performed this experiment. Blackness started after 4 to 7 seconds. After 10 to 16 seconds the whole visual field was black. The last remnant of vision was a small central island. Six subjects noted darkness first in the nasal part of the visual field. One was not able to tell where it started. Vision returned immediately when the finger was removed. I have also performed this experiment on myself several times and seen the central island of retained vision soon followed by complete blackness. I am not sure however where blackness begins. I could not in this way provoke the scotoma I have described in this paper nor could the other subjects.

Arterial emboli are a common cause of retinal ischemia.

A 70 year old man with hypertension (160/100 mm) during the last two months once or twice a week had had attacks of blindness in his right eye. All attacks were identical. At onset there was blurring of vision. The first time he thought that his glasses were moist. He wiped them but his sight was not improved. Then there was complete blindness in the right eye starting on the nasal side. The last area with retained vision was located at the temporal border of the right visual field. Vision returned in the opposite direction. First a small part of the temporal field reappeared. Then normal vision rapidly spread in the nasal direction. He had taken the time with a stopwatch. Each attack lasted twenty minutes. He had not measured the time from onset to complete blindness but estimated it to be a few seconds. He used the word blackness but when I questioned him closer he said that the colour was perhaps more grey than black. On one occasion we had the opportunity to examine his eyegrounds during an attack. The arteries were empty and did not pulsate. The veins were wide and dark red. The diagnosis was transitory ischemic attacks. Angiography showed thrombosis in the right carotid artery. At operation an arteriosclerotic plaque with a fresh thrombosis in the internal carotid artery near the bifurcation was removed.

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The difficulty of obtaining an accurate history agrees with my experience. For this reason I suppose that Walsh's description at least in part is based on the observations made during experimentally provoked blackout.

My auto observations differ from the visual disturbances provoked by a cervical cuff, centrifugation, ophthalmodynamometry pressure with the finger on

the eye or an embolus. The reason is perhaps that my scotoma develops in "slow motion" during a few minutes while the blurring and blackness in the experiments develops rapidly during a few seconds. My scotoma may be identical with the first phase in the experiments ("blurred vision"). However I am not quite satisfied with this interpretation because it fails to explain why slight pressure on the eye does not provoke the scotoma. My main intention though was to describe the scotoma even if there still are problems to solve.

Because my scotoma is positive I believe that it is due to ischemia in the retina. If I did not sit or lie down the next event probably would be blackness and loss of consciousness. I have avoided this experiment however because it might be dangerous.

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OPHTHALMOLOGIC AND GENETIC ASPECTS
OF WILSON'S DISEASE
(Hepatolenticular Degeneration)

BY

ANNI KARMA

The study comprised two pairs of siblings with Wilson's disease and the 44 family members living in the same locality. Ophthalmologic examination as well as determination of serum copper and caeruloplasmin concentration were performed on all subjects. In the patients with Wilson's disease a liver biopsy specimen was examined by light microscopy.

The last of the four cases had no physical sign of the disease.

In the three symptomatic patients the finding that led to the diagnosis was the Kayser-Fleischer ring. The asymptomatic patient had no such ring.

It seems that Kayser-Fleischer ring probably develops within the months neurologic symptoms become manifest. The copper ring disappears gradually during years of penicillamine treatment.

The consanguinity of the two families was shown by a genealogical study and evidenced an autosomal recessive inheritance of the disease.

Key words: Kayser-Fleischer ring - cornea - Wilson's disease - hepatolenticular degeneration

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Wilson's disease or hepatolenticular degeneration is a rare hereditary disorder of copper metabolism and is characterized by degenerative changes particularly in the brain and liver (Wilson 1912)

The primary defect in this inborn error of metabolism is unknown. The hepatic cells evidently are affected with a disorder in the incorporation of copper into caeruloplasmin. Free copper in the plasma is increased and copper accumulates everywhere in the tissues.

The destructive effect of the copper is greatest in the liver, the basal ganglia and cortex of the brain and the kidneys. The result is liver dysfunction, neurological and psychic symptoms indicating a central nervous system lesion and alteration of the renal function.

A visible sign of an increase of copper in the organism is a ring in the corneal periphery at the level of Descemet's membrane. The ring was first described by Kayser in 1902. Fleischer in 1912 discovered its connection with Wilson's disease. The ring has since proved to be the only pathognomonic physical sign in Wilson's disease.

Hall in 1921 was the first to discover the autosomal recessive inheritance of the disease. It has subsequently been confirmed by numerous studies (Bearn 1960).

Since 1960 the disease has been treated with penicillamine (Walshe 1956). Penicillamine is highly cupriuretic but the ultimate mechanism of action is unknown. Penicillamine has improved the prognosis of the disease. The drug has a favourable effect on the neurologic symptoms while no certain influence on hepatic dysfunction has been recorded (Sternlieb & Scheinberg 1964).

Material and Methods

There are five patients with Wilson's disease in Finland at present* and most probably they represent the total number of cases since any case reported is treated free of charge.

The present study comprised four patients with Wilson's disease and 44 family members. The patients are two pairs of siblings and the families all live in Northern Finland in the same locality, Ylivieska. The fifth patient lives in Southwest Finland and was unavailable for the study.

* National Pensions Institute Statistical Office June 30 1972

The eyes of the family members were examined and the caeruloplasmin and copper values of their serum were determined. In the patients with Wilson's disease thorough biochemical analyses and an examination of liver biopsy specimen with light microscope were performed. The two families affected with Wilson's disease were subjected to a genealogical investigation**.

Case Reports

Case 1

Wilson's disease was diagnosed in 1960 in a 19 year old girl (Helsinki University Hospital). Her case has been published previously (Hillbom 1961). At the time of the diagnosis the patient's disease had been manifest for at least three years and had reduced her to a completely helpless condition owing to severe rigidity, tremor and dysphagia.

The diagnosis was based on the verification of the Kayser Fleischer ring in 1960.

Since June 1961 the patient has taken an average of 1 900 mg penicillamine daily. Her neurologic symptoms have improved dramatically. She can move normally and lead a normal life. Despite the therapy symptoms of hepatic injury began to appear in 1964 when an enlargement of the spleen and an increased haemorrhagic disposition were noted.

The patient's eyes were examined by the present author in March 1972. Only a small superior crescent was found in both corneas. Evidently the ring must have diminished.

Case 2

The same disease was diagnosed in 1964 in the 24 year old brother of Case 1 (Helsinki University Hospital).

The brother's symptoms from the outset were less marked than those of his sister. They were manifested in general slight rigidity, slight tremor and occasional convulsions.

The patient has regularly taken a mean daily dose of 1 200 mg penicillamine since the diagnosis of the disease.

In this patient also the Kayser Fleischer ring was the diagnostic observation. In the eye examination in February 1972 I found that the rings had disappeared completely.

Case 3 (own case)

The patient was a man of 29 who had had neurologic symptoms since June 1969. He had increasing tremor in the upper and lower limbs. His speech had become dysarthric and dysphagia was present from time to time.

The patient had been examined three times during the autumn of 1969 at the Neurologic Department of Oulu Central Mental Hospital and the condition was defined as essential tremor although the clinical picture showed atypical features.

In December 1969 the patient visited our Out Patient Clinic of Ophthalmology for the first time complaining of his pupils which in the last few months had become distinctly larger.

The patient held himself stiffly and had a tremor in both upper and lower limbs. The tremor was aggravated in intention and momentary jerky agitated attacks of tremor occurred. The facial muscles showed little movement. The speech was dysarthric, the handwriting shaky. The patient's skin was unusually brown. He perspired profusely.

Examination of the eyes revealed that the pupils were clearly unusually large in respect of the lighting. They reacted to light but even after constriction they remained abnormally large. Microscopic examination revealed no pathologic findings in the media. The visual acuity was normal. The abnormality of the pupils was evidently due to the antispasmodic treatment the patient was receiving.

In April 1970 the patient visited the Out Patient Clinic of Ophthalmology for a follow up examination. The pupils had returned to normal size after the anticholinergic effect of the medicine was over. The other neurologic symptoms had not changed.

This time microscopy revealed a typical circumferential brown greenish Kayser Fleischer ring in the periphery of both corneas at the level of Descemet's membrane and ending at the Schwalbe's line. The ring was granular in character and deposits were arranged in two parallel zones separated by a clearer zone. No pathological pigmentation was noted in the other parts of the eye.

The diagnosis was Wilson's disease. It was confirmed by the laboratory results and the liver biopsy findings. The caeruloplasmin concentration of the serum was greatly decreased to 3 IU/l by paraphenylenediamineoxidase method and no caeruloplasmin could be demonstrated at all when tested by the immunoelectrophoretic method. The serum copper was abnormally low: 12-24 $\mu\text{g}/100\text{ ml}$. The amount of copper in 24 hour urine exceeded 200 μg .

Liver biopsy sections showed granular fatty infiltration and by rubeanic acid staining some copper particles though they were not very numerous.

The patient has now taken penicillamine for 2½ years the mean dose being 1900 mg a day. The tremor has decreased and dysphagia has completely disappeared.

In the eye examination in September 1972 the Kayser Fleischer rings were distinctly visible. The granular character and the two separate zones of the ring were even more distinctly visible than before.

Case 4 (own case)

An analysis of the laboratory findings for family members revealed that the previous patient's sister aged 26 had no caeruloplasmin at all in the serum. This was checked by various methods.

The serum copper content was decreased 63 $\mu\text{g}/100\text{ ml}$ and copper excretion in 24 hour urine increased 110 μg .

The patient is in good condition and symptom free. She has no Kayser Fleischer ring.

The liver biopsy section showed distinct pathological degenerative changes. In this case a knowledge of the quantity of copper in the patient's liver would have been very helpful. However it has been considered too hazardous to take a new liver biopsy since the prothrombin value of the plasma had fallen permanently to a pathological level.

The patient's diagnosis is not in doubt although so far there have been no symptoms of Wilson's disease.

Penicillamine therapy with a daily dose of 900 mg was instituted in October 1972.

Discussion

The unique diagnostic value of the Kayser Fleischer ring has not decreased with the years. In no other disease has there been discovered a bilateral brownish greenish ring of granular structure which borders on Descemet's membrane and ends at Schwalbe's line.

The Kayser Fleischer ring is an early symptom and is usually always found by the time clinical neurological symptoms appear. It is therefore strange that the copper ring of the patient diagnosed in April 1970 was not seen until 10 months after the disease had become manifest. The ring evidently developed during the follow up time of four months.

It is probable that the liver protects the organism against copper damage for a long time but once the hepatic copper trapping mechanism is saturated symptoms of copper toxicity arise in various parts of the organism (Sternlieb & Scheinberg 1968; Goldstein et al 1968). At the same time possibly at a rapid rate the Kayser Fleischer ring also becomes visible. This theory is supported by the symptom free patient of the series who has no Kayser Fleischer ring.

It is known (Brand & Takats 1951; Uzman & Jakus 1957) that the copper content in the stroma of the entire cornea of a patient with Wilson's disease is high. Accumulations of copper particles have been found in the anterior lens capsule and in the vitreous humour (Rix et al 1965).

No visible signs of copper other than the Kayser Fleischer ring of the eyes were found in the present patients.

The Kayser Fleischer ring diminishes in the course of penicillamine treatment. The remnant of the Kayser Fleischer ring in the upper part of the cornea in the patient who had the longest history of treatment reinforces the many earlier observations according to which the ring disappears last from the region of the vertical axis (Sussman & Scheinberg 1969). Reduced intensity of the ring and remission of the symptoms are not chronologically intercorrelated (Sternlieb & Scheinberg 1964). The three present patients with symptoms have been receiving treatment for periods varying from 2½ to 11 years which suggests that the ring diminishes slowly during the course of several years.

Penicillamine treatment must be instituted also in asymptomatic patients as soon as the diagnosis is definite. There is hope that the treatment once instituted will prevent the manifestation of the disease in the asymptomatic patient of the series (Sternlieb & Scheinberg 1968).

Cytological research (Fig 1) suggests an autosomal recessive inheritance of the disease (Hall 1971; Bearn 1960). The parents of the brother and sister diagnosed by the present author were found to have a common ancestor from the 18th century. The ancestry of the two families with Wilson's disease had

In December 1969 the patient visited our Out Patient Clinic of Ophthalmology for the first time complaining of his pupils which in the last few months had become distinctly larger.

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Liver biopsy sections showed granular fatty infiltration and by rubeanic acid staining some copper particles though they were not very numerous.

The patient has now taken penicillamine for 2 1/2 years the mean dose being 1500 mg a day. The tremor has decreased and dysphagia has completely disappeared.

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Case 4 (own case)

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Penicillamine treatment must be instituted also in asymptomatic patients as soon as the diagnosis is definite. There is hope that the treatment once instituted will prevent the manifestation of the disease in the asymptomatic patient of the series (Sternlieb & Scheinberg 1968).

Cenealogical research (Fig. 1) suggests an autosomal recessive inheritance of the disease (Hall 1921; Bearn 1960). The parents of the brother and sister diagnosed by the present author were found to have a common ancestor from the 18th century. The ancestry of the two families with Wilson's disease had

been united in the 17th century. A common gene has thus been traced for all the four patients with Wilson's disease.

Parish registers revealed that there were a few large families in which almost all the children had died young of an unknown disease (Fig. 1 VI/1-2-3). A number of them may have been homozygous for the "gene of Wilson's disease".

Another pathologic caeruloplasmin value 11 IU/l in addition to that of the symptom-free person with Wilson's disease, was also discovered (Fig. 1). This person is probably a heterozygous carrier of the "gene of Wilson's disease". Ten per cent of the heterozygotes are found to have a low serum caeruloplasmin (Sternlieb & Scheinberg 1968). This explains why no more frequent low values were noted in the serum.

The district from which the present Wilson patients come is a genetic isolate. Heterozygotes in regard to the "gene of Wilson's disease" are surely more numerous there than elsewhere in Finland where migration of the population has been greater.

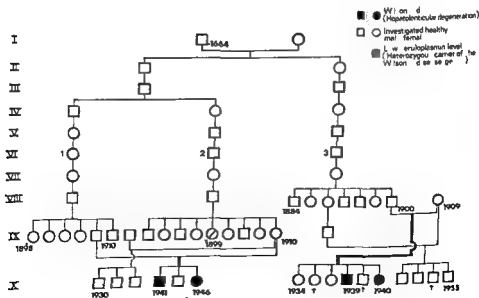


Fig. 1
Pedigree of the two families with Wilson's disease

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been united in the 17th century. A common gene has thus been traced for all the four patients with Wilson's disease.

Parish registers revealed that there were a few large families in which almost all the children had died young of an unknown disease (Fig. 1 VI/1-2-3). A number of them may have been homozygous for the gene of Wilson's disease.

Another pathologic caeruloplasmin value 11 IU/l in addition to that of the symptom free person with Wilson's disease was also discovered (Fig. 1). This person is probably a heterozygous carrier of the "gene of Wilson's disease". Ten per cent of the heterozygotes are found to have a low serum caeruloplasmin (Sternlieb & Scheinberg 1968). This explains why no more frequent low values were noted in the serum.

The district from which the present Wilson patients come is a genetic isolate. Heterozygotes in regard to the "gene of Wilson's disease" are surely more numerous there than elsewhere in Finland where migration of the population has been greater.

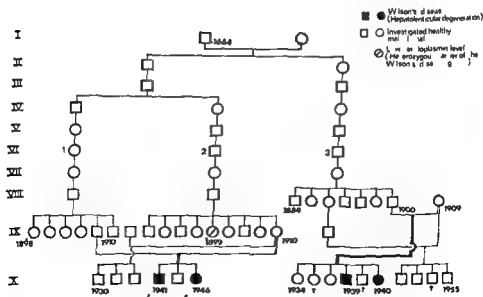


Fig. 1
Pedigree of the two families with Wilson's disease

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RECORDINGS OF APPLANATING FORCE AT CONSTANT INTRAOCULAR PRESSURE

V Intraocular volume changes due to changes in the content of aqueous humour

BY

WILLIAM THORBURN

Facility of outflow of aqueous humour estimated at two P_i levels suggests a pressure dependence within the eye with a lower facility of outflow at a higher pressure level. A rise in the intraocular pressure by 15 mmHg before the measurement of the facility of outflow resulted in larger values. No age dependent difference in the facility of outflow between eyes of selected young and elderly subjects with normal ocular tension was found. Nor could any difference be established between subjects with normal ocular tension and those with ocular hypertension. In young subjects accommodation induced an increase in the facility of outflow. Thirty minutes after a single dose of pilocarpine no significant decrease in intraocular pressure but an increase in facility of outflow was found. Two hours after a single dose of acetazolamide a decrease in intraocular pressure but no significant change in facility of outflow was found.

Key words: acetazolamide, applanation, constant intraocular pressure, facility of outflow, force recording, intraocular pressure, pilocarpine, tonography.

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The continuous steady increase in displaced volume observed during the continuous recording of the applanating force at constant intraocular pressure is considered to be due to increased outflow of aqueous humour. It was the aim of the present study to apply the present method (37-38) to estimate the facility of aqueous outflow and to study the influence of a change in the outflow pressure in the untreated eye. The intraocular pressure and the facility of aqueous outflow in different groups of subjects were studied.

It was further considered of interest to study possible changes in the facility of outflow induced in different ways. Thus accommodation was used as an experimental tool and the influence of two drugs pilocarpine and acetazolamide was investigated. Only a short time effect of a single dose in young subjects has been studied, i.e. a detailed pharmacological investigation is not included.

Materials and Methods

Three different groups of subjects were studied (for details see ref. no. 39). Young subjects aged between 23 and 29 years: the total number of the unselected group was 13 subjects (group A); elderly subjects with normal ocular tension aged between 50 and 73 years: 51 subjects (group B); and elderly subjects with ocular hypertension with or without other signs of glaucoma aged between 51 and 83 years: 67 subjects (group C).

1 Tonography according to Grant¹⁴

Tonography was performed routinely. The intraocular pressure was measured in the supine position with a Draeger handheld appplanation tonometer. The tonography was performed with a standardized electrical Schiøtz tonometer. The right eye was always

Abbreviations

- ΔV change in displaced volume
- P_i intraocular pressure in the undisturbed eye measured with a Schiøtz tonometer
- P_1 initial reading by appplanation tonometry
- P_2 final reading by appplanation tonometry
- P_e intraocular pressure during the experiment
- C facility of outflow determined by use of a Schiøtz tonometer
- C_p facility of outflow determined by recordings of appplanating force at constant intraocular pressure
- C_{p10} , C_{p20} determined at a P_e of 6 and 10 mmHg respectively added to the P_i
- C_p pupillary facility
- P_{pvc} peripheral venous pressure
- t time in minutes
- F flow of aqueous humour

examined before the left eye. The P_o and the facility of outflow (C_{sch}) were determined by use of tonographic tables with the assumption of average ocular rigidity and normal radius of the cornea (18)

2 Recordings of applanating force at constant intraocular pressure

The experiments have been carried out with an apparatus which measures continuously the applanating force and which at the same time keeps the intraocular pressure at a nearly constant and known level. The apparatus and the procedures used on living human eyes are described elsewhere (37-38). The applanated area was calculated according to the Imbert Fick law from the applanating force and the intraocular pressure. The displaced volume can be estimated in different ways. In the present study it was calculated as if it was a spherical segment with a radius of 8 mm and the base area equal to the applanated area. Briefly the experimental procedures were as follows. With the subject in sitting position the intraocular pressure was measured repeatedly by applanation tonometry and the stabilized reading (P_a) was accepted as the intraocular pressure on which the choice of P_t was based. The above apparatus was then applied and recording of the applanating force was performed with $P_t = P_a + 6$ mmHg for three minutes. Without interrupting the recording the P_t was raised to $P_a + 10$ mmHg for another three minutes and finally a short recording with $P_t = P_{a2} + 15$ mmHg was made (ascending pressure steps). Recording of the applanating force was also performed using the same P_t values in the opposite order i.e. starting with a short recording at $P_{a2} + 15$ mmHg followed by a three minutes recording at $P_a + 10$ mmHg and so on (descending pressure steps). The change in displaced volume at each intraocular pressure change represents the volume pressure relationship and changes in the intraocular volume occurring at constant intraocular pressure can be estimated. For a special purpose recording of applanating force over a longer time with only one P_t level was performed (see below).

Using recordings of applanating force at constant intraocular pressure the facility of outflow expressed in $\mu\text{l/mmHg/min}$ is computed according to the equation

$$C_{cp} = \frac{\Delta V}{t(I - P_a)}$$

C_{cp6} and C_{cp10} are the calculated facilities at the P_t levels 6 and 10 mmHg respectively added to the P_a . The symbol ΔV represents the difference between the displaced volumes at the start and at the end of each P_t level (38). No correction due to a change in P_e is introduced.

To study the influence of accommodation the method of recording applanating force with ascending pressure steps was used. The undisturbed eye was fixed on a distant mark through a -4 D glass added to the refractive error of the eye. Only one level of accommodation was studied. The subject was asked to keep the fixation mark clear during the whole recording.

To study the influence of the drug pilocarpine which is cholinergic one drop of 2% pilocarpine hydrochloride dissolved in water was instilled in the lower conjunctival sac. The lower eyelid was pulled downwards for one minute to avoid loss through the punctum. The change in refractive error was followed and reached its maximum after about 30 minutes. Twenty minutes after the drop was instilled measurement of the

intraocular pressure was started. The recording of applanating force was begun when refraction did not increase any further (26-32 minutes after the drug was instilled in the eye).

To study the influence of the drug acetazolamide which is an inhibitor of carbonic dehydrase 500 mg of the drug (Diamox® Lederle) was given orally with some water. Two hours later recording of applanating force was begun.

The short time effects of the above drugs were studied after administration of a single dose in young subjects by use of recordings of applanating force with ascending pressure steps. At least three days were allowed between experiments with the different drugs on the same subject.

As discussed in a previous paper(33) it was from some recordings impossible to estimate any continuous increase in the displaced volume with sufficient accuracy. In that case the recording was rejected. The present results except those concerning effects of accommodation and drugs are based on the recordings of applanating force in which both pressure levels were accepted.

All the subjects producing experimental results which had to be discarded for various reasons were compared with the remaining subjects in groups B and C as regards sex, age and intraocular pressure distribution. No systematic selection could be detected.

When several accepted recordings from a subject (group A) were present the figures of one recording chosen at random were used in the comparisons.

To test the significance of the difference between two measurements on the same eye the *t* test for paired observations was used. The differences are presented as confidence intervals (level 0.95) for differences of means. Within each subject group the differences between different measurements of facility of outflow are presented as the simultaneous confidence intervals (level 0.95) for differences of means * as are the differences between the three groups of subjects analysed by use of the method of multiple comparisons in a multivariate analysis of variance. The variances within and between eyes were discerned by a model of analysis of variance.

Results

Facility of outflow at different outflow pressures in untreated eyes

1. Repeated recordings of applanating force with ascending pressure steps were performed on the right eyes of young subjects (group A). The results are presented in Table I. The calculated mean C_{10} is greater than the mean C_{15} . The variance of the C_{15} is greater than that of C_{10} . The total variance and

The confidence intervals include the true difference between the means with the chosen probability of 0.95. If the confidence interval includes zero no statistically significant difference between the means is obtained using a two sided test at the 5% significance level.

Simultaneous confidence intervals involve a constant probability for all true differences under study not only for each one singly(33).

examined before the left eye. The P_o and the facility of outflow (C_{ef}) were determined by use of tonographic tables with the assumption of average ocular rigidity and normal radius of the corner (18)

2 Recordings of applanating force at constant intraocular pressure

The experiments have been carried out with an apparatus which measures continuously the applanating force and which at the same time keeps the intraocular pressure at a nearly constant and known level. The apparatus and the procedures used on living human eyes are described elsewhere (37-39). The applanated area was calculated according to the Imbert-Fick law from the applanating force and the intraocular pressure. The displaced volume can be estimated in different ways. In the present study it was calculated as if it was a spherical segment with a radius of 7.8 mm and the base area equal to the applanated area. Briefly the experimental procedures were as follows. With the subject in sitting position the intraocular pressure was measured repeatedly by applanation tonometry and the stabilized reading (P_a) was accepted as the intraocular pressure on which the choice of P_t was based. The above apparatus was then applied and recording of the applanating force was performed with $P_t = P_a + 6$ mmHg for three minutes. Without interrupting the recording the P_t was raised to $P_a + 10$ mmHg for another three minutes and finally a short recording with $P_t = P_a + 15$ mmHg was made (ascending pressure steps). Recording of the applanating force was also performed using the same P_t values in the opposite order i.e. starting with a short recording at $P_a + 15$ mmHg followed by a three minutes recording at $P_a + 10$ mmHg and so on (descending pressure steps). The change in displaced volume at each intraocular pressure change represents the volume pressure relationship and changes in the intraocular volume occurring at constant intraocular pressure can be estimated. For a special purpose recording of applanating force over a longer time with only one P_t level was performed (see below).

Using recordings of applanating force at constant intraocular pressure the facility of outflow expressed in ml/mmHg min. is computed according to the equation

$$C_{ef} = \frac{11}{t(P_t - P_a)}$$

C_{ef6} and C_{ef10} are the calculated facilities at the P_t levels 6 and 10 mmHg respectively added to the P_a . The symbol 11 represents the difference between the displaced volumes at the start and at the end of each P_t level (38). No correction due to a change in P_a is introduced.

To study the influence of accommodation the method of recording applanating force with ascending pressure steps was used. The undisturbed eye was fixed on a distant mark through a -4 D glass added to the refractive error of the eye. Only one level of accommodation was tried. The subject was asked to keep the fixation mark clear during the whole recording.

To study the influence of the drug, pilocarpine which is cholinergic one drop of 2% pilocarpine hydrochloride dissolved in water was instilled in the lower conjunctival sac. The lower eyelid was pulled downwards for one minute to avoid loss through the punctum. The change in refractive error was followed and reached its maximum after about 30 minutes. Twenty minutes after the drop was instilled measurement of the

force with ascending pressure steps. Both the C_{cp} and the C_{cp10} were larger than when ascending pressure steps were applied. The variance within eyes is about the same as that obtained with ascending pressure steps but the total variance is numerically slightly increased. From each subject one random experiment of each kind was chosen and confidence intervals (level 0.95) for differences between means of outflow facility are presented in Table III.

3 Continuous recordings of applanating force over a long time and with one and the same P_i level were performed on the eyes of three young subjects with known smooth recordings. The displaced volume was calculated for every third minute. The results are presented in Fig. 1. In one recording no tendency towards a change of the increase in displaced volume per time unit with increasing time was found while in the other two experiments a slight tendency towards a leveling out of the increase was observed. No definite conclusions concerning ΔV and time can be drawn.

4 The intraocular pressures and the facilities of outflow in the three groups of subjects were investigated. Appplanation tonometry in a sitting position

Table II

Facility of outflow at two P_i levels (C_{pr} and C_{cp10}) calculated from recordings of applanating force with descending pressure steps. Right eye of 8 subjects from the group in Table I.

Subject	No of recordings	Facility of outflow $\mu\text{l/mmHg/min}$			
		C_{pr}		C_{cp10}	
		mean	range	mean	range
1	"	0.51	0.50-0.51	0.27	0.21-0.37
4	"	0.45	0.47-0.43	0.36	0.33-0.39
6	"	0.35	0.25-0.44	0.33	0.22-0.44
7	1	1.06		0.63	
8	"	0.19	0.1-0.30	0.30	0.29-0.31
9	"	0.29	0.46-1.11	0.34	0.29-0.39
10	"	0.46	0.39-0.53	0.34	0.30-0.37
11	"	0.33	0.31-0.44	0.23	0.2-0.34
Mean		0.47		0.37	
S_u		0.036		0.006	
S_T		0.05		0.013	

S_u Variance within eyes S_T total variance

Table I

The facility of aqueous outflow ($\mu\text{l}/\text{mmHg}/\text{min}$) at two P_t levels (C_{cp6} and C_{cp10}) calculated from recordings of applanating force with ascending pressures steps and from one tonogram obtained with a Schiotz tonometer (C_{sch}) Right eye of 13 young subjects (group A)

Subject	No of recordings	Facility of outflow $\mu\text{l}/\text{mmHg}/\text{min}$				
		C_{cp6}		C_{cp10}		C_{sch}
		mean	range	mean	range	
1	3	0.25	0.15-0.39	0.24	0.19-0.30	0.91
2	2	0.35	0.32-0.37	0.10	0.08-0.12	0.98
3	2	0.16	0.15-0.17	0.18	0.13-0.22	0.97
4	3	0.48	0.21-0.67	0.21	0.20-0.24	0.34
5	1	0.55		0.39		0.49
6	3	0.36	0.23-0.51	0.22	0.16-0.28	0.96
7	2	0.33	0.32-0.34	0.29	0.27-0.30	0.39
8	2	0.31	0.19-0.43	0.25	0.15-0.34	0.11
9	3	0.44	0.15-0.73	0.24	0.13-0.39	0.91
10	3	0.43	0.23-0.75	0.23	0.26-0.31	0.44
11	1	0.60		0.27		0.37
12	2	0.31	0.22-0.39	0.20	0.14-0.23	0.33
13	1	0.34		0.23		0.31
Mean		0.38		0.24		0.51
S_w		0.036		0.005		-
S_T^2		0.036		0.006		0.003

S_w Variance within eyes S_T^2 total variance

the variance within eyes are about equal at each P_t -level. Subject no. 2 with a myopia of -19 D showed a very low value of C_{cp10} and a marked difference between C_{cp6} and C_{cp10} . The facility of outflow determined with a Schiotz tonometer (C_{sch}) falls between the C_{cp6} and C_{cp10} and its total variance is about the same as that of C_{cp10} .

2 Repeated recordings of the applanating force with descending pressure steps were performed on eight subjects from the above group with known smooth recordings i.e. small slow oscillatory changes of the intraocular volume. The results of the experiments are presented in Table II. Of the subjects only one (no. 8) had a larger facility of outflow at the higher intraocular pressure level. In the remaining seven subjects there was a lesser facility of outflow at the higher intraocular pressure level as found in the recordings of applanating

force with ascending pressure steps. Both the C_{cp6} and the C_{cp10} were larger than when ascending pressure steps were applied. The variance within eyes is about the same as that obtained with ascending pressure steps but the total variance is numerically slightly increased. From each subject one random experiment of each kind was chosen and confidence intervals (level 0.95) for differences between means of outflow facility are presented in Table III.

3. Continuous recordings of applanating force over a long time and with one and the same P_t level were performed on the eyes of three young subjects with known smooth recordings. The displaced volume was calculated for every third minute. The results are presented in Fig. 1. In one recording no tendency towards a change of the increase in displaced volume per time unit with increasing time was found while in the other two experiments a slight tendency towards a leveling out of the increase was observed. No definite conclusions concerning ΔV and time can be drawn.

4. The intraocular pressures and the facilities of outflow in the three groups of subjects were investigated. Applanation tonometry in a sitting position

Table II

Facility of outflow at two I_t levels (C_{p6} and C_{p10}) calculated from recordings of applanating force with descending pressure steps. Right eye of 8 subjects from the group in Table I.

Subject	No of recordings	Facility of outflow $\mu\text{l/mmHg/min}$			
		C_{p6}		C_{p10}	
		mean	range	mean	range
1	"	0.51	0.50-0.51	0.97	0.21-0.59
4	"	0.45	0.47-0.48	0.36	0.33-0.38
6	2	0.35	0.95-0.44	0.33	0.77-0.44
	1	1.06		0.63	
8	"	0.19	0.17-0.90	0.30	0.99-0.31
9	"	0.79	0.46-1.11	0.34	0.29-0.38
10	"	0.46	0.39-0.53	0.34	0.30-0.37
1		0.33	0.31-0.44	0.93	0.97-0.34
Mean		0.47		0.36	
S_w		0.036		0.006	
S_T		0.075		0.013	

S_w Variance within eyes S_T total variance

Table III

Confidence intervals (level 0.95) for differences between mean values (\bar{D}) of the facility of outflow (G_{cp6} G_{cp10}) calculated from recordings of applanating force with descending pressure steps (Table II) and ascending pressure steps (Table I)

	\bar{D}	CI
G_{cp6}	0.27	0.09 to 0.45
G_{cp10}	0.16	0.04 to 0.27

\bar{D} mean difference CI confidence intervals

resulted within each group in a mean difference between right and left eye of 0.4 mmHg or less. Of the P_0 -values calculated from the initial part of the tonograms obtained with a Schiötz tonometer the value of the second investigated eye was on an average 1.5 mmHg lower. This is a wellknown phenomenon (15). Table IV presents all results of the first investigated eye. The mean

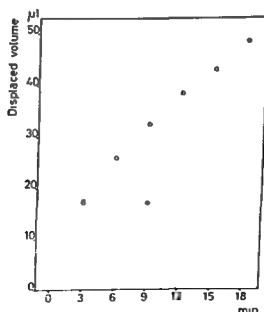


Fig. 1

Displaced volume calculated every third minute during longrun recordings of applanating force at one P_t level. ● = Subject no. 6 $P_t = P_a + 6$ mmHg ○ = Subject no. 10 $P_t = P_a + 7$ mmHg × Subject no. 12 $P_t = P_a + 10$ mmHg

Table IV

The intraocular pressure in the right eye of the three groups of subjects measured with a Schiøtz tonometer (P) under the assumption of an average coefficient of ocular rigidity of 0.015 and with applanation tonometry in the sitting position initial reading (P_i) and after repeated measurements (P_a)

Group		P	P_{ai}	P_a	$P_{ai}-P_a$
A	n	13	13	13	13
	mean	13.5	15.9	13.6	1.5
	SD	2.8	3.3	2.7	1.6
B	n	51	49	51	42
	mean	16.2	17.4	14.7	2.0
	SD	3.3	3.8	3.0	1.8
C	n	67	47	67	47
	mean	20.6	23.1	21.2	2.3
	SD	3.7	4.3	3.9	1.5

n = number of subjects SD = standard deviation.

Table V

Facility of outflow ($\mu\text{l}/\text{mmHg}/\text{min}$) in the right eye of the three groups of subjects calculated from tonograms obtained with a Schiøtz tonometer (C_{sA}) under the assumption of an average ocular rigidity ($uncorr$) and recalculated with C_A corrected for ocular rigidity and calculated from recordings of applanating force with ascending pressure steps (C_{p6} C_{p10})

Group		C_A	C_{sA}	C_{p6}	C_{p10}
A	mean	0.31	0.33	0.33	0.03
	SE	0.03	0.03	0.06	0.02
B	mean	0.29	0.03	0.34	0.04
	SE	0.03	0.03	0.03	0.01
C	mean	0.9	0.9	0.33	0.02
	SE	0.03	0.01	0.03	0.01

n = number of subjects SE = standard error of the mean.

Table III

Confidence intervals (level 0.95) for differences between mean values (\bar{D}) of the facility of outflow (C_{cp6} C_{cp10}) calculated from recordings of applanating force with descending pressure steps (Table II) and ascending pressure steps (Table I)

	\bar{D}	CI
C_{cp6}	0.27	0.09 to 0.45
C_{cp10}	0.16	0.04 to 0.27

\bar{D} mean difference CI confidence intervals

resulted within each group in a mean difference between right and left eye of 0.4 mmHg or less. Of the P_o -values calculated from the initial part of the tonograms obtained with a Schiötz tonometer the value of the second investigated eye was on an average 1.5 mmHg lower. This is a wellknown phenomenon (15). Table IV presents all results of the first investigated eye. The mean

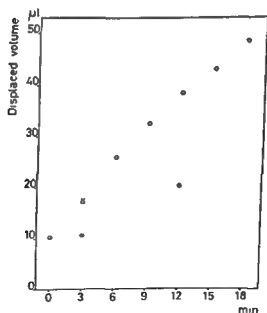


Fig. 1

Displaced volume calculated every third minute during longrun recordings of applanating force at one P_t level. ● = Subject no. 6 $P_t = P_a + 6$ mmHg ○ = Subject no. 10 $P_t = P_{a2} + 7$ mmHg × Subject no. 12 $P_t = P_a + 10$ mmHg

Table VII

Simultaneous confidence intervals (level 0.95) for differences between mean values of the groups A, B and C obtained by a multivariate analysis of variance. The intervals are given for the variables which showed a difference between the groups by use of a univariate analysis. Group A: 13 subjects; group B: 27 subjects; group C: 23 subjects.

Variable	A-C	B-C
P_1	-12.3 to -2.8	-10.5 to -2.6
P	-11.9 to -3.3	-9.4 to -2.9
$C_{A \cup B}$	-0.07 to 0.21	-0.03 to 0.16

established concerning C_{cp} and C_{cp0} . Simultaneous confidence intervals for the differences between the mean values of the groups is given in Table VII. Obviously only group C differed from groups A and B. As the difference between corrected and uncorrected C_{cp} was very small, the corrected C_{cp} was not analysed statistically.

Summing up the results under point 4 we find that within all groups of subjects the facility of outflow estimated by means of recordings of applanating force at constant intraocular pressure was influenced by the outflow pressure. No influence was found to be due to age of the subjects (groups A and B) nor was any difference due to ocular hypertension (group C) established. On the other hand, the facility of outflow determined from tonograms with a Schiotz tonometer showed a tendency towards lesser values in the group C as compared to the groups A and B.

Table VIII

Confidence intervals (level 0.95) for differences between mean values of the change in facility of outflow (C_{p0} and C_{p10}) induced by accommodation, calculated from recordings of applanating force with ascending pressure steps.

	n	No accom- modation mean	During accommodation 4 D mean	Mean difference	C.I.
C_{p0}	13	0.35	0.49	0.14	-0.05 to 0.33
C_{p10}	13	0.1	0.33	0.16	0.10 to 0.23

n: number of subjects; C.I.: confidence intervals.

difference between P_{01} and P_{02} is about the same in all groups of subjects and of the magnitude of 1.5–2.3 mmHg

The facility of aqueous humour outflow was determined from tonograms obtained with a Schiötz tonometer (uncorrected C_{sch}). Within each group the average C_{sch} of the right eye was numerically larger (0.02 ul/mmHg/min) than that of the left eye but the difference was not significant. The tonograms were then recalculated according to observed ocular rigidity which was obtained from the difference between applanation tonometry in recumbent position and the P_0 (corrected C_{sch} for details see ref. no. 30). The figures from the right eyes are presented in Table V. The average ocular rigidity within each group was found to be very close to the value 0.0215 and the correction only affected the mean value of the estimation of the facility of outflow to a small not significant extent. In the same table are shown the facilities of outflow at two P_1 -levels (C_{cpe} and C_{cpt0}) in the right eye calculated from recordings of applanating force with ascending pressure steps. C_{cpe} and C_{cpt0} were about the same for both eyes. The mean C_{cpe} is in all groups larger than the mean C_{cpt0} (for simultaneous confidence intervals for the differences between mean values see Table VI).

Between the three groups of subjects a difference in the values of applanation tonometry and in the uncorrected C_{sch} appeared. No difference was

Table VI
Simultaneous confidence intervals (level 0.95) for the differences between some mean values from Table V within the groups A, B and C

Group		$C_{cpe} - C_{cpt0}$	$C_{sch \text{ uncorr}} - C_{sch \text{ corr}}$
A $n = 15$	\bar{D}	0.11	-0.03
	SE	0.05	0.01
	CI	-0.04 to 0.29	-0.07 to 0.04
B $n = 30$	\bar{D}	0.10	0.01
	SE	0.02	0.01
	CI	0.03 to 0.17	-0.03 to 0.06
C $n = 30$	\bar{D}	0.16	0.00
	SE	0.03	0.01
	CI	0.06 to 0.25	-0.03 to 0.03

n number of subjects \bar{D} mean difference SE standard error of the mean
CI confidence intervals

The effect of accommodation on the facility of outflow

The C_{ps} and C_{epio} during accommodation were compared with the values of the same eye without accommodation. Increased facility of outflow was found during the period of accommodation. For results and confidence intervals (level 0.95) for the differences between mean values see Table VIII.

Effects of pilocarpine and acetazolamide on the facility of outflow

The effects of pilocarpine on intraocular pressure and on facility of outflow are presented in Table IX. There was no significant change in the intraocular pressure in this short time experiment, but the facility of outflow increased at both pressure levels. The mean increase in refractive power was 4.1 diopters. No obvious correlation between the increase in refractive power and in facility of outflow was found.

The results of administration of acetazolamide are presented in Table X. There was decrease in the intraocular pressure, but no significant change in the facility of outflow.

DISCUSSION

The blood volume of the human eye is not known. Becker & Friedenwald(4) considered it to be over 900 μ l. Several animal experiments have been performed, but no direct method of measuring the total blood volume of the untouched human eye has been reported. Compared with the considerable turn over of blood during a few minutes, the measurable change of aqueous humour content during tonographic experiments is very small. It is not possible to distinguish the change in intraocular volume due to a change in aqueous humour content from that due to a change in blood content. All results concerning calculations of aqueous humour dynamics must then be evaluated with great caution.

The continuous increase in displaced volume calculated from the recordings of applanating force primarily depends on the facility of aqueous humour outflow, the net inflow of aqueous humour, and the change in the blood content. In addition, there may be other causes, such as a change in scleral distention. If there is a pressure dependent decrease in the net inflow of aqueous humour and no time dependence, a constant P_i results in a constant flow of aqueous humour during the experiment. The decrease in the net inflow of aqueous humour then appears as an increase of the facility of outflow.

Table I\

Effects of pilocarpine on the intraocular pressure (P_{a1} P_a) and on the facility of outflow (C_{ep6} C_{ep10}) 30 minutes after one drop of 2% solution of the drug was administered. Recordings of applanating force with ascending pressure steps were used. Confidence intervals (level 0.95) for differences between mean values are given.

	n	Before treatment mean	After administration of pilocarpine mean	Mean difference	CI
P_{a1}	11	15.4	14.5	1.1	-0.9 to 3.0
P_a	12	13.7	14.1	0.4	-2.2 to 1.4
C_{ep6}	12	0.36	0.67	0.31	0.11 to 0.50
C_{ep10}	12	0.21	0.42	0.20	0.1 ^a to 0.3 ^s

n number of subjects CI confidence intervals

Table \

Effects of acetazolamide on the intraocular pressure (P_{a1} P_a) and on the facility of outflow (C_{p6} C_{ep10}) two hours after oral administration of 500 mg of the drug. Recordings of applanating force with ascending pressure steps were used. Confidence intervals (level 0.95) for differences between mean values are given.

	n	Before treatment mean	After administration of acetazolamide mean	Mean difference	CI
P_{a1}	12	15.4	12.4	3.0	1.2 to 4.8
P_a	12	13.7	11.1	2.6	1.5 to 3.7
C_{ep6}	10	0.37	0.32	0.06	-0.01 to 0.09
C_{ep10}	12	0.22	0.21	1.1	-0.9 to 3.0

n number of subjects CI confidence intervals

the effect of a possible deformation besides the appplanation of the cornea is included. These calculations resulted in an average increase of the C_{cp6} -value by about 20 % and of the C_{p10} value by about 10 %. None of these methods of calculation gives definite information on the volume displaced by appplanation in the living eye.

A systematic overestimation of the appplanated area(37) will introduce a proportional error. By converting the appplanated area to a displaced volume according to the relationship between base area and volume such an error will to a greater extent affect the calculated displaced volume corresponding to large areas and thus result in an overestimation mainly of the C_{p10} value at ascending pressure steps. The experiments with descending pressure steps indicate that this error can be neglected.

The error caused by calculating the displaced volume by assuming it to correspond to a spherical segment with a radius of 7.8 mm instead of the real radius of the cornea is insignificant compared with other errors.

Errors due to the outflow pressure The addition in outflow pressure to the normal one is the difference between P_i and the pressure of the untouched eye under the assumption of an unchanged episcleral venous pressure (P). The relation between the pressure in the eye during a tonographic experiment and that of the untouched eye is discussed by Goldmann(12). In the present study the reading after repeated appplanation measurements (P) was accepted as the intraocular pressure of the untouched eye. The P was measured with a Draeger appplanation tonometer and the validity of the readings are similar to those made with a Goldmann tonometer(6-10). The accuracy of the P_i determination is discussed in a previous paper(37). As it was found in the calibration experiments performed on enucleated human eyes that the variance between eyes accounted for about 80 % of the total variance repeated experiments on the same eye were expected to reduce the influence of the error of the P_i determination on the estimation of the facility of outflow. However the variances of C_p within eyes and the total variance were about the same as discussed above (page 40⁷). Obviously the dynamic condition of the living eye introduces considerable uncertainties. It was assumed that the error of the P_i determination within one and the same eye was about the same at different P levels. The values of C_{p6} and C_{p10} may then be compared within the same eye. The errors in the determinations of P and P_i have a greater influence on the C_{p6} -value than on the C_{p10} -value.

The change of P caused by a force acting on the eye is a matter of concern. Using Schiötz tonometer Iinner(25) found an average increase of 1.25 mmHg



defined as pseudofacility(2) Assuming the facility of outflow and the pseudo facility both are linear to the outflow pressure there is no possibility to distinguish between these by use of the present method alone. It was presumed that the net inflow of aqueous humour and blood content of the eye would not show any systematic changes during each part of an experiment with a constant P_i .

Recordings of applanation force at constant intraocular pressure has demonstrated considerable variation in the calculated facility of outflow (Table I). The fact that the variances within eyes and the total variance was about the same indicates that the variation is mainly due to the present method of estimating facility of outflow. As shown in a previous paper(40) large slow changes in the intraocular volume were found probably due to changes in the content of the vascular bed. Oscillatory changes of the intraocular volume of a magnitude of more than 10 μ l have been observed. Using the P_i level $P_a + 6$ mmHg such a volume change corresponds to a computed C_{eff} value of more than 0.5 μ l/mmHg/min. Even in the recordings used in the present study slow changes of the intraocular volume probably due to other causes than aqueous dynamics affect the calculations of the facility of outflow. It must be borne in mind that the experimental situation is far from the normal one with an almost complete elimination of the spontaneous changes in intraocular pressure occurring in the undisturbed eye and with stepwise sudden changes of the intraocular pressure during the experiments. The selection of the recordings was based on the possibility to estimate a continuous steady slope of the tracing of the applanating force i.e. the continuous increase in displaced volume per unit of time(38). The general significance of the selection is however so far not possible to evaluate as no conclusions can be drawn from the subjects which were not available for investigation by the present method.

Errors in the estimation of the change in displaced volume (ΔV) The error induced at conversion of the applanated area to a displaced volume by treating the latter as spherical segment is not known. As discussed in a previous paper (37) this method of calculating the displaced volume results in figures expressing the volume in a relative unit as they are estimated by indirect means. Compared with the results of investigations of the relationship between applanated area and displaced volume obtained from enucleated eyes this method of calculation probably represents the bottom limit value. This must be kept in mind when the figures obtained with the present method are compared with those obtained with a Schiotz tonometer. The recordings of applanating force were evaluated according to the experimental results of Innér(29) in which

Hypothetical time dependence of the net inflow of aqueous humour

In recordings with descending pressure steps the difference between C_{cpr} and C_{pr} was about the same as with ascending pressure steps but the mean facility of outflow was larger at both P_i levels compared with the results from recordings with ascending pressure steps (Table III). This was not expected and the reason is not at all clear. One possible explanation may be mentioned. Pseudofacility has previously been described in monkeys(3, 5) and is determined in man by Kupfer & Sandereson(22) and by Goldmann(13). The impossibility of differentiating a change in aqueous humour flow from a change in blood volume must again be stressed. Assuming that the difference between the values of ascending and descending pressure steps is due to the turnover of aqueous humour there is possibly not only a pressure dependent but also a time dependent decrease in the net inflow of the aqueous humour. With descending pressure steps the sudden increase of intraocular pressure from P_i by 15 mmHg would result in a partial arrest of the net inflow of aqueous humour which only slowly recovers. In two subjects the long run recording of applanating force showed a slight tendency towards leveling out the increase in displaced volume with increasing time (Fig. 1). This might as well be due to a slow recovery of the net inflow of aqueous humour.

Dependence of the facility of outflow on the outflow pressure

Decrease in the facility of outflow with increasing intraocular pressure was suggested in 1933 by Becker & Friedenwald(4). In the enucleated human eye increasing resistance of outflow with increasing intraocular pressure is reported by Ellingsen & Crant(8). They worked with a range of intraocular pressure which greatly exceeded that used in the present study. Furthermore conclusions drawn from experiments with enucleated eyes must be applied with very great caution to the living eye(19).

All results of the present study concerning the calculated facility of outflow show the same tendency as those reported by Moses(16). Using a constant pressure applanation tonography based on a Mackay-Marg tonometer he studied healthy eyes with the subject in supine position but otherwise as in this study. He found indications that facility of outflow was greater at low pressures than at higher pressures. He did not report any difference between results of ascending and descending pressure steps.

In addition to the study by Moses a demonstration of the influence of P_i level on facility of outflow in man *in vivo* was attempted by Levene & Hyman (11). Using tonography with a Schiotz tonometer and scleral impression they found a decreased facility of outflow at increased pressure. The sudden in

in the P_e caused by the weight of the tonometer. The plunger weight, the intraocular pressure and the age of the subject were not found to have any significant influence on the increase in P_e due to the tonometer weight. Neither miotics nor acetazolamide induced a significant change in P_e (27). In the present study varying applanating force was used from about 5 g and upwards. It is not known to what extent small forces acting on the eye affect the P_e , nor what kind of relationship exists between the force and the change in P_e , besides that a loading of the eye with 16.5 g and 21 g both increase the P_e with about 1.95 mmHg (26). No correction due to a change in the P_e was introduced. However if a proportional increase of P_e with increasing applanating force to 1.25 mmHg at 16.5 g is assumed a nearly proportional increase of both C_{cp6} and C_{cp10} by about 15% occurs.

Errors due to the method. The difference in the calculated facility of outflow at two P_e levels shows that the C_e -value at the higher pressure level is smaller compared to that at the lower pressure level. Using ascending pressure steps several reasons for this result might be suggested.

Firstly the increasing applanated area may increase the resistance of outflow. Moses (34) reported a reduced facility of outflow in enucleated human eyes when the diameter of the applanated area exceeded about 6 mm. In a clinical study using living human eyes the same author also found that a reduction of the facility of outflow appeared in all cases when the applanation diameter was greater than 9.4 mm (35). In the experiments of the present study the largest applanated area used for calculations of facility of outflow had a smaller diameter than 9.4 mm. Furthermore by using the method with descending pressure steps the diameter of the applanated area varied within about the same range at both pressure levels used for tonographic purpose and the effect of increasing applanation on the facility of outflow was avoided. The difference between C_{cp6} and C_{cp10} was about the same as with ascending pressure steps (Table I and II).

Secondly an increase in the intraocular pressure may cause a slow flow of fluid from the tissue to the vessels until a new state of equilibrium is achieved. This would result in an overestimation of ΔV in the initial part of an experiment. A slow scleral distention (32) might contribute to the initial increase in displaced volume and result in a similar error. The recordings of applanating force performed during 15 minutes suggest that these errors do not play any important role in relation to the observed variation in the facility of outflow. The similarity of the difference between C_{cp6} and C_{cp10} in experiments with ascending and those with descending pressure steps furthermore indicates that these factors do not play any important role.

routes is reduced at the higher P_i level compared with the flow at the lower P_i level. The magnitude of the hypothetical flow in the subjects with ocular hypertension (group C) becomes larger than in the subjects with normal ocular tension (group B) specially at the lower P_i level. The validity of this way of calculating the aqueous flow is not possible to evaluate.

Independence of the facility of outflow of the intraocular pressure in the untouched eye

In two groups of subjects of similar age but representing two different levels of intraocular pressure (group B and C) the magnitude of the observed facility of outflow at both P_i levels (C_{cp} and $C_{p/10}$ in Table V) was about equal. These results indicate that the difference in intraocular pressure level cannot be due to the facility of outflow alone. A difference between the groups B and C in P_i of a magnitude of 5-6 mmHg could explain the result but so far no evidence for such a possibility has been reported(11, 20, 25, 26). Previously the groups B and C have been studied with regard to the volume pressure relationship which includes the rapid expulsion of blood at stepwise increases in the intraocular pressure(39) and to intraocular volume changes considered due to the content of the vascular bed(40). Nothing was found in these experiments indicating that a systematic difference in the change of the blood content within the eye between the groups B and C could be responsible for the present results.

Comparison between the results obtained with Grant's tonography and with recordings III appanaling force at constant intraocular pressure

The magnitude of the facility of outflow calculated from a tonogram obtained with a Schiotz tonometer from the first investigated eye agrees in general with the $C_{p/10}$ obtained with ascending pressure steps (Table V). The errors in the calculation of the displaced volume in the present method are discussed above (page 40). The inconsistent difference that generally exists is mostly marked in young subjects. But with descending pressure steps the $C_{p/10}$ was increased for group A to a value exceeding that of the tonography with a Schiotz tonometer (Table II).

A decrease in the facility of outflow with increasing age is previously described by Lindholm et al (24) and by Johnson(14) basing their observations on measurements with a Schiotz tonometer. Such a decrease in facility of outflow with increasing age was not observed in experiments using constant intraocular pressure (groups A and B in Table V). Possible errors in Grant's tonography(14) were previously discussed(4, 12, 31). The present method is thought to give a better estimation of facility of outflow than methods with changing intraocular pressure. Very little is known about the change in intra

crease in intraocular pressure might cause changes in the blood content of the eye uncertainty in the calculation of the facility of outflow is unavoidable. However the results of these authors are in good accordance with those of the present study.

Short time experiments on selected subjects thus indicate that the facility of outflow *in vivo* is dependent on the outflow pressure within the same eye (Table V). The results agree with those of previous investigations obtained with the different techniques mentioned above. The effect of decreasing facility of outflow with increasing intraocular pressure then tends to stabilize the rate of aqueous flow through the trabecular meshwork and makes it independent of the outflow pressure.

Calculations of flow of aqueous humour based on facility of outflow and outflow pressure

Assuming that the flow of aqueous humour through the conventional outflow routes is proportional to the outflow pressure and that C_{P_1} and P_c are constant during the experiments the flow (F) can be calculated according to the equation

$$F = (C_{P_1} - C_{P_c}) \times (P_1 - P_c)$$

Calculations of F are based on the mean values of the facility of outflow obtained in the present study (Table V) the corresponding mean P_1 level C_{P_1} of 0.06 $\mu\text{l}/\text{mmHg}/\text{min}$ for in young subjects (group A)(19/22) C_{P_1} of 0.03 $\mu\text{l}/\text{mmHg}/\text{min}$ for in elderly subjects (groups B and C)(19) and P_c of 9 mmHg (21). The results of this calculation are collected in Table VI. In all the three groups of subjects the hypothetic aqueous flow through conventional outflow

Table VI

Hypothetic aqueous humour flow in $\mu\text{l}/\text{min}$ through conventional outflow routes in the three groups of subjects calculated according to the equation $F = (C_{P_1} - C_{P_c}) \times (P_1 - P_c)$. The mean values of the facility of outflow at two P_1 levels (C_{P_1} and $C_{P_{10}}$) from Table V. C_{P_1} 0.06 $\mu\text{l}/\text{mmHg}/\text{min}$ for group A and 0.03 $\mu\text{l}/\text{mmHg}/\text{min}$ for groups B and C. P_c 9 mmHg.

Group	Mean P_a	$P_1 = P_a + 6 \text{ mmHg}$	$P_1 = P_a + 10 \text{ mmHg}$
A	13.6	19.4	23.3
B	14.1	19.6	23.3
C	20.9	26.2	30.1

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The experimentally induced changes in facility of outflow

The effect of accommodation on the facility of outflow (Table VIII) agrees with the previous findings of Armaly & Burian(1) of increased facility of outflow during accommodation. The effects of pilocarpine and acetazolamide on the facility of outflow in the present investigation were as could be expected (16). There was no significant drop in intraocular pressure after the pilocarpine administration in spite of the increased facility of outflow (Table IX). However a decrease in intraocular pressure following pilocarpine administration is first evident after 60 minutes(9). It is reasonable to assume that the lack of intraocular pressure change is due to additional effects caused by the drug. In the short term experiment with acetazolamide no significant change in the facility of outflow was found (Table X). The observed decrease in intraocular pressure is compatible with a reduction of the net inflow of aqueous humour which is in agreement with previous studies.

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ON THE OCCURRENCE OF PSEUDO EXFOLIATION MATERIAL
IN EXTRABULBAR TISSUE FROM PATIENTS
WITH PSEUDO EXFOLIATION SYNDROME OF THE EYE

BY

AMUND RINGVOLD

The present communication demonstrates pseudo exfoliation material in the palpebral conjunctiva of patients with pseudo exfoliation syndrome of the eye as determined by slit lamp examination. Biopsies of the skin or the oral mucous membrane of these patients did not reveal pseudo exfoliation material by electron microscopic investigation. Such material was also absent in conjunctival biopsies from patients without pseudo exfoliation syndrome of the eye. It is concluded that the pseudo exfoliation material in the mucous membrane of the eyelids is obviously not transported into this region from the intraocular space and hence the occurrence of such material in this location indicates that pseudo exfoliation material is synthesized both in ocular and in extrabulbar tissue in patients with pseudo exfoliation syndrome of the eye.

Key words: eye - conjunctiva - connective tissue - histology - ultrastructure - pathology

The pseudo exfoliation syndrome (PE syndrome) is characterized by the presence of a light grey substance (PE material) at different locations within the anterior segment of the eye observed by slit lamp examination (for review Nasved 1969). It has been established that many eyes showing this

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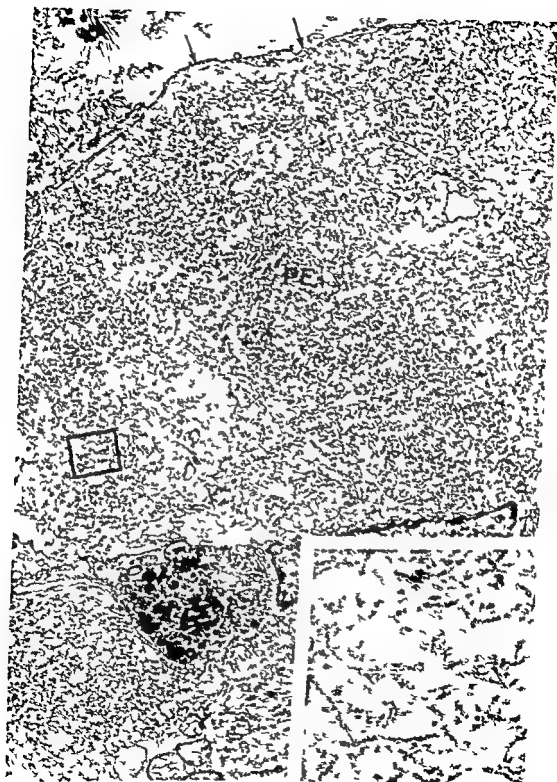
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syndrome later develop increased intraocular tension (Hansen & Sellevold 1969) Hence the appearance of such material may represent a presage of glaucoma and as such the condition is of considerable value in clinical ophthalmology The clinical findings concerning the distribution of PE material within the eye have been verified by light and electron microscopic investigations and by means of these techniques additional information has been obtained (for ref see Ringvold & Vegge 1971)

Recent studies revealing PE material in the limbal conjunctiva (Ringvold 1971) prompted the present investigation which was undertaken in order to see whether PE material occurs beyond the bulbus proper in patients showing the PE syndrome of the eye

Material and Methods

A total of 11 patients provided specimens for this study The patients had been admitted to hospital for ocular surgery (one eye was enucleated because of persistent pains caused by capsular glaucoma the other 10 eyes were operated for senile cataract)

Seven of the patients showed bilateral PE syndrome by slit lamp examination and they were 67 73 73 74 75 86 and 89 years old at the time of operation Only two of these cases were under treatment for glaucoma After retrobulbar anesthesia a biopsy was obtained from the palpebral conjunctiva five of the specimens were taken from the intermedial part of the inferior palpebra 1-2 mm below the margin whereas the remaining two were derived from the intermedial part of the superior palpebra corresponding to the upper tarsal edge Prior to the performance of biopsies from skin and mucous membrane the tissue was infiltrated with local anesthetics (2% Xylocain/Exadrin) Three skin biopsies from different persons were obtained one from the upper lid one from the lower lid and one from the volar side of the forearm In addition two biopsies from the mucous membrane of the lower lip were available One of these is derived from one of the three patients mentioned above the other was taken from a fourth person

The remaining four patients showed no sign of PE syndrome by slitlamp

Fig 1

Electron micrograph showing large masses of PE material (PE) in the palpebral conjunctiva Note thin cytoplasmic processes (arrows) surrounding the PE aggregate at the upper left $\times 6900$ Lower right inset higher magnification of the boxed area $\times 40000$



examination (examined in mydriasis) and apart from a senile cataract the eyes appeared normal. These patients were 65, 69, 72 and 82 years old at the time of the operation. Conjunctival biopsies were taken from the superior and the inferior palpebra from one and three of these patients respectively. As a control iris tissue from all of these eyes was prepared for electron microscopy.

All specimens were immediately placed in precooled 1-2% OsO_4 adjusted to pH 4 with either cacodylate or phosphate buffer. Tissue blocks were dehydrated in graded acetone solutions and embedded in Taab or Spurr's embedding resins. Sections were made with an LKB Ultratome and stained with aqueous solutions of uranyl acetate and lead citrate. Siemens Elmiskop 1 and 1A were used.

Results

Palpebral conjunctiva PE material was found in six of the seven specimens from patients with PE syndrome of the eye: i.e. in four biopsies from the inferior and in two biopsies from the superior palpebra. The material was composed of numerous straight irregularly outlined fibrils measuring 80-950 Å in diameter and they appeared identical to PE fibrils as seen in sections from intraocular tissue (Bertelsen et al 1964; Ashton et al 1965; Ringvold 1970). Only few membrane bound granules were observed among the fibrils. The amount of PE material varied considerably from one specimen to another. Thus some of them were very rich in such material (Fig 1) showing large masses of it in all tissue blocks whereas in other specimens only moderate or small amounts were seen. Mostly the PE material appeared as aggregates lying among the normal connective tissue components. However in some sections particularly in those showing such material in abundance collagen fibrils and elastic fibers were present also within the PE aggregates. Frequently the aggregates of PE material were more or less surrounded by long thin cytoplasmic processes from neighboring cells (Fig 1). In some cases invaginations of connective tissue cells were seen to contain PE fibrils in a disorderly arrangement. PE material was also observed in considerable amounts around vessels infiltrating the endothelial basement membrane (Fig 2). How

Fig

The electron micrograph shows great amounts of PE material (PE) partly infiltrating the endothelial basement membrane (arrow). E endothelial cell, L vessel lumen. $\times 15,500$. Lower right inset: higher magnification of the boxed area $\times 60,000$.

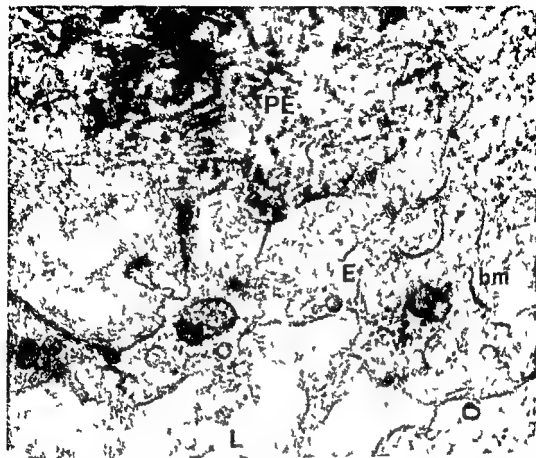


Fig 3

PE material (PE) seen in close apposition to the endothelium filling out an impression (arrow) on the cell surface E endothelial cell L vessel lumen bm basement membrane
 x 60 000

ever the basement membrane was not completely interrupted as known from iris vessels in eyes with PE syndrome (Ringvold 1969). In some regions PF material was found in close apposition to the endothelium filling out impressions on the cell surface (Fig 3).

In the specimens from patients without PF syndrome no PF material was found in the conjunctiva. The investigation of the iris tissue which was prepared as a control did not reveal PF material in any of these eyes.

Skin and mucous membrane of the lower lip PE material was not observed in any of these specimens.

DISCUSSION

So far the PE syndrome has been considered a purely ocular disorder since no change in any other organ associated with this syndrome has been observed. This view was recently questioned in a report showing PE material in the limbal conjunctiva (Ringvold 1972). However this finding did not rule out the possibility that PE material had been transported into the limbal conjunctiva from the intraocular space since the bulk of aqueous humour is drained through this region.

The present demonstration of PE material in the mucous membrane of the eyelids must be considered conclusive evidence that this material also originates in extrabulbar tissue because the palpebral conjunctiva is exposed neither to the aqueous humour nor to the venous blood from the anterior part of the bulb. The notion that it should have been transported into the eyelids from the intraocular space over the systemic circulation seems far fetched.

The fact that the palpebral conjunctiva in one of the PE syndrome cases did not show the PE material is not conclusive. The amount of PE material in the other six eyes varied considerably from one specimen to the other and it was also unevenly distributed within each specimen. Thus this case may demonstrate that some patients with PE syndrome of the eye have no PE material in the conjunctival palpebra or it may indicate that the biopsy was too small.

The specimens from skin and oral mucous membrane did not show PE material. This finding does not prove that the material is absent from such locations. Rather it should stimulate further search for PE material in extrabulbar tissue.

Acknowledgments

All specimens used in this study were obtained from the University Eye Department Rikshospitalet Oslo. I wish to express my sincere thanks to Professor Thore Lie Thomassen and the members of his staff for providing the material.

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Potts Albert M (ed) The Assessment of Visual Function The C V Mosby Company
St Louis 1972 926 pages 102 illustrations Price \$ 94 50

The aim of the present book is to emphasize the connection between basic science and ophthalmology. To the Scandinavian reader the term basic science most often denotes the tight woven complex of mathematics physics chemistry and statistics which constitutes the tool for the ultimate analysis of the biological processes. The common substance in all chapters is however the classical clinically oriented visual physiology.

The topics are 1) visual acuity and visual field 2) rod vision and clinical aspects of night vision 3) color vision of normal observers and abnormal color vision and 4) special topics including practical aspects of depth perception electrophysiological measurements and evaluation of glare dynamic visual acuity and changes with aging.

The book offers the best of the American didactic traditions with a lucid and diverting style and abundant illustrations. My personal preference is the chapter on the various visual acuities by Melvin L. Rubin - a veritable *tour de force* in a difficult matter and always carefully related to everyday clinical practice with the Snellen letters. References to the original literature are placed after each chapter.

The buyer will get a concise refresher course in the topics mentioned but in a library with a suitable and up to date collection of textbooks and monographs the book can hardly be considered absolutely necessary.

Erik Krogh

Vollagen Karl Der Augenarzt Vol 2 VEB Georg Thieme Leipzig 1979 1940 pages
573 illustrations Price DM 145

The present second volume of *Der Augenarzt* is the second revised edition of this 9 volume's handbook of ophthalmology.

The contents of this second edition are somewhat different from those of the first in that this new version concerns itself exclusively with the eyes functioning and investigations thereof.

The optical section and the description of the eye as an optical instrument have been placed in the hands of a physicist which has resulted in a considerable overemphasis of the theoretical and mathematical aspects.

In addition to a reworking of the description of the usual investigative methods this edition has also included the use of ultrasound and up dated the discussion on methods of electroculography.

This book thus appears as a unified explanation of investigative methods and techniques for evaluating the eyes function and in this regard the book is completely adequate although it will be difficult for readers lacking familiarity with the German language to gain access to its information.

Unfortunately developments in the medical world are so rapid that such giant works as this reference book naturally cannot keep up and perhaps it may well be that the value of the book is therefore not proportional to the enormous amount of work and the considerable expense associated with its publication.

Jens Edmünd

Bochart Hannelore Die Augenarzthelferin Ein Notizbuch für die Praxis F. K. Schattauer Verlag Stuttgart - New York 1972 205 pages Price DM 19.80

The demand for ophthalmological paramedical auxiliary personnel is becoming more and more urgent and has during the past few years manifested itself in the release of numerous "cookbooks" for ophthalmological assistants. The present publication is a small handy easy to use pocketbook which undoubtedly will be an outstanding first aid for the eye specialist's secretary and nurses.

F. Creerien

Bergsma Daniel (ed.) Birth Defects Atlas and Compendium The National Foundation March of Dimes The Williams & Wilkins Company Baltimore 1973 1 006 pages with 641 illustrations

This book consists of three sections. The first is an extensive pictorial display including 115 pictures in colour and 526 in black and white, the second a short clinical description of 542 diseases and genetic markers and the third a number of tables. The purpose of the volume is to assemble any anatomic or functional variant from the normal range in homo sapiens which is inherited by any Mendelian mode of transmission or caused by fresh mutation, any chromosomal abnormality or by any infectious chemical or physical insult to the embryo or foetus prior to birth. Although 340 contributors have assembled the entries, the opus appears homogenous thanks to a rigid editorship which has made the book an excellent reference work.

The illustrations are well printed and indicate clearly the salient features of the diseases in question. It is a pity that not all diseases or syndromes mentioned can be found in the pictorial atlas but that will probably be remedied in the next edition. Eye diseases are well represented. A novelty in a medical textbook is the emphasis on diagnostic clues found in the oral cavity, most physicians should be able to improve their diagnostic register by looking at the illustrations of this area.

It may be regretted that the pictures of the normal fundus represent only light Caucasian eyes when in fact the majority of the world's population has a dark skin.

The compendium gives the most common synonyms of each disease mentions differential diagnoses and proceeds with a clinical description, aetiology, pathogenesis, genetic prognosis, treatment and features in heterozygotes. All entries are followed by short bibliographic notes of which most are new and relevant. The compendium is intended for physicians of many countries and the diseases are therefore indexed in English, French, German and Spanish. The text is in English and so are practically all the references.

This volume is a major interdisciplinary approach. It is important for the physician who detects an unknown malformation or birth defect and who can plan a direct and time saving diagnostic programme for the patient. In this respect it is unsurpassed by other textbooks.

The ophthalmological contributions are highly informative and offer most of present day knowledge of hereditary diseases in childhood and early adult life. Hereditary diseases in later years are included in a few instances. The text is concise and very comprehensive in spite of the limited space available. Mistakes are very difficult to find and I have found only a single inconsistency. There is a mention of Retinal Aplasia

which states that Leber's congenital amaurosis is not included under this heading and one on the *Amaurosis Congenita of Leber* which includes congenital retinal aplasia in the indexed synonyms. Most ophthalmologists will presumably regard the two terms as identical. Omissions are very few indeed. I have been unable to find the Laurence-Moon-Bardet-Biedl syndrome, Leber's optic atrophy and the not uncommon dominant infantile optic atrophy.

The third section comprises a number of tables of diagnostic and prophylactic value. It is characteristic of the aim of the book that the first table is concerned with genetic risks. There are a number of tables outlining our present knowledge of metabolic disorders, their heredity, diagnoses, therapy and prenatal diagnosis. A couple of tables give information of clefting syndromes. These have not been easily accessible before and they will be of great help in differential diagnosis. I am convinced that tables presenting syndromes with corneal dystrophies, congenital cataracts and tapetoretinal degenerations would be equally informative and suggest that such tables be incorporated in the second edition.

The book is provided with an impressive index consisting of 80 pages with three columns each. All syndromes and diseases mentioned as synonyms can be found here but unfortunately not all those which are listed as differential diagnoses. This is sometimes a nuisance since taxonomy has evidently been the editor's hardest job.

I found it very difficult to find the entry for congenital glaucoma. After having looked through the 18 references to glaucoma I found it at long last in the Italian and French entries under *glaucoma congenito* and *glaucoma congenitale*. Night Blindness in the index refers to the Nougaret type while the entry *Stationary Night Blindness* refers to an article including both the dominant (Nougaret) and the autosomal recessive types as well as the linked type with myopia. With use however the book becomes familiar and it becomes quite easy to find the information required.

This atlas and compendium will be a standard reference book and can be recommended to all clinical departments in mental hospitals and laboratories concerned with diagnostic evaluations.

Mette Warburg

Smith J. Lawton. *Neuro Ophthalmology* Volume VI. Symposium of the University of Miami and the Bascom Palmer Eye Institute 1977. 914 pages with 128 illustrations. Price \$ 75.50.

The sixth volume of *Neuro ophthalmology Symposium of the University of Miami and the Bascom Palmer Eye Institute* contains valuable articles concerning such neuro-ophthalmic topics as therapy of thyroid eye disease, clinical retinal function testing for hereditary retinal disease, management of optic glioma in childhood, anatomy of the cavernous sinus, neuro-ophthalmics of transtentorial herniation, isolated ophthalmic migraine, the pupil in syphilis and flebography in orbital diagnosis as well as several papers of a casuistic character. An article on management of acute optic neuritis recommends high dose short term steroids. All articles include references. The book ends with a mixed author index and a comprehensive subject index (including medications in the case report).

The volume like the earlier ones in the same series should have a place in every ophthalmic library.

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flavimaculatus (Newell Krill & Farkas) and electron microscopy in histopathologic diagnosis (Zimmerman, Font Ts'o & Fine)

The third section contains a symposium on microsurgery of the outflow channels. The participants include such pioneers as Krasnov (sinusotomy) Dannheim and Cairns (trabeculotomy) Spencer (histologic evaluation) Grant (laboratory research) Becker Podos & Asseff (clinical research) and Schaffer who wrote the conclusions.

The book's final section consists of a symposium on the genetics of ophthalmology. The symposium includes an introduction by Goldberg *in vitro* techniques by Hsia biochemical detection of inborn errors by Cotlier ocular anomalies in malformation syndromes by Opitz and genetic counseling by Cross.

The book is very well edited and makes its appearance as a parade of stars both with regard to its authors and in terms of the subject matter and can be most warmly recommended as one of the year's good buys.

E Gregersen

Ishihara's Design Charts for Colour Blindness For illiterate persons 8 pages Price Dkr 92 50 Isshinkai Foundation Japan 1960 Distributor for Scandinavia A A Reitzel Ltd Copenhagen

This short set of plates provides a practical tool for detecting colour deficiencies in illiterate persons particularly in children. The design is the well known pattern consisting of symbols printed on a confusing background. Instead of numerals however geometrical figures (circles squares and curved lines) are used.

The book contains as accessories two cardboard printed in black and white to illustrate the shape of the symbols in use and in addition a marten hair brush to be used in tracing the curved lines without impairing the print.

This set of plates seems to be very useful in genetic research making even the screening of children possible because the Ishihara lay out is more selective than the similarly designed American Hardy Rand and Ritter set. The Ishihara set however lacks screening plates for detecting blue yellow deficiencies which are valuable when dealing with acquired colour deficiencies. The design charts are too few to be useful for licensing purposes.

1 Dreyer

Axelfeld/Pau Lehrbuch und Atlas der Augenheilkunde 11. Aufl. Gustav Fischer Verlag Stuttgart 1963 XIV 749 pages 125 figures 14 x 24 cm Price DM 190

The 8th edition of Axelfeld's *Lehrbuch und Atlas der Augenheilkunde* (1933 by Hertel) was the first textbook the present reviewer studied just before starting his education in ophthalmology. Many a colleague in this area has done the same and we found this a good choice. The new edition (by Pau 1963) has been completely revised and appears as a modern precise didactic textbook to be warmly recommended to all who are about to start their ophthalmologic education to the specially interested student to the general practitioner and to the ophthalmologist himself when needing brief information. A condition for use is an understanding of the German language.

The textbook is built up in chapters classically arranged in topographic order - each written by an outstanding colleague.

P Brandstrup

Contemporary Ophthalmology Selected Proceedings of the American Academy of Ophthalmology and Otolaryngology Annual Meeting September 1961 The C. V. Mosby Company Saint Louis 1962 246 pages Price \$21.50

A number of ophthalmology's best most competent experts are found herein discussing some of ophthalmology's most pertinent subjects. The book presents in an ordered profusion some of the newest advancements in present day ophthalmology along with outposts of future ophthalmology.

The first and second parts include the following topics: the eye in malignant hypertension (Ashton) surgery of the dislocated lens (Barriquer) pigment epithelium in macular disease (Cowan) ophthalmic drug therapy (I opold) drusen and fundus

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CONGENITAL HEREDITARY BILATERAL NON ATTACHMENT OF RETINA A Sibship of Two

BY

C I PHILLIPS D A LEIGHTON and R M FORRESTER

A brother and sister the only two children of non consanguineous parents have bilateral microphthalmos degenerative corneal opacities shallow anterior chambers and in the anterior vitreous white masses like cotton wool with some large blood vessels. Excision of the mass from the vitreous cavity of one eye showed surprisingly normally developed detached retina round a core of fibrous condensed vitreous. Otherwise the children are normal and have the normal male and female karyotype.

A very similar sibship has been reported by Franceschetti (1956) - a brother and sister children of first cousins being affected the consanguinity of these parents supports our suggestion that a recessive inheritance explains the abnormalities in our cases. No evidence of heredity exists in the similar case described by Magnus (1927) or in the group of possibly similar cases of *retinal dysplasia without systemic involvement* described by Reese & Straatsma (1955) but our cases may well belong to the same category also our cases may represent examples of an extreme form of *falciform retinal folds*.

Key words: retina - detachment of retina - heredity - malformations

Cases of congenital non attachment of the retina without other ocular or systemic abnormalities are rare (Duke Elder 1964). Accordingly a brother and sister with bilateral involvement seem to be worth reporting especially as they

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VARIA

International Symposium on the Eye and Systemic Disease

The Department of Ophthalmology of the University of Iowa Iowa City Iowa will sponsor an International Symposium on the Eye and Systemic Disease to be held in Iowa City November 15-17 1973. An excellent international faculty composed of ophthalmologists internists and a dermatologist will discuss important practical relationships between ocular disease and systemic disease. For further information contact Frederick A. Mausolf M.D. Symposium Chairman Department of Ophthalmology University Hospitals Iowa City Iowa 52242.

Neuro Ophthalmology Course

Bascom Palmer Eye Institute University of Miami

The Bascom Palmer Eye Institute Department of Ophthalmology University of Miami School of Medicine will conduct the annual Neuro Ophthalmology Course January 7-10 1974. The meeting will be held at the new Sonesta Beach Hotel Key Biscayne Miami Florida. The faculty will include Dr. Douglas R. Anderson Dr. Alan C. Bird Dr. Ronald M. Burde Dr. Robert B. Daroff Dr. Noble J. David Dr. Joel S. Claser Dr. William F. Hoyt Dr. Simmons Lestell Dr. Edward W. D. Norton Dr. Norman J. Schatz Dr. Peritz Scheinberg Dr. J. Lawton Smith. The Course is designed to present basic and clinical material in Neuro Ophthalmology for the practitioner and trainee in Ophthalmology Neurology and Neuro Surgery. Major topics include I Functional Anatomy of the Visual System II Oculo Cerebrovascular Disease III The Patient with Diplopia. For further information or requests for registration Neuro Ophthalmology Course P.O. Box 815 Biscayne Annex Miami Florida 33157.

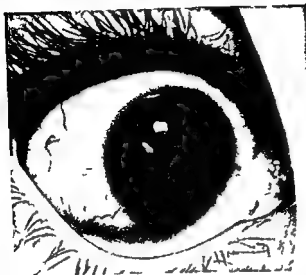


Fig 1

Case 1 Girl aged 10 years Right eye Difficult to examine and photograph Small eyeball and shallow anterior chamber Oblique band of corneal opacity

Right Behind the lens was a fairly dense white opacity which looked like fluffy cotton wool and in which some large blood vessels were visible No details behind the level of the anterior vitreous could be seen

Left Appearance as in the right eye but on the nasal side a red reflex could be faintly seen On the iris infero temporal to the irregular pupil was a small white mass See Fig 2

In the slight hope that some vision might be achieved a right lens extraction and radical vitrectomy were done

Pathological report Histological examination showed that the mass in the vitreous consisted principally of bunched up retina well vascularised and with a basically normal architecture including stretches of the outer nuclear layer and bordering external membrane Condensed vitreous formed the base of the pyramid of tissue it was relatively fibrous and was permeated by a number of vessels concentrated near the internal aspect of the retina and running down into the narrow approximated folds Included in the periphery was some non pigmented epithelium from the region anterior to the ora serrata showing a little erratic proliferation and folding together with a channel of direct communication whereby it ran inwards for a short distance attached to the periphery of the vitreous A smaller separate piece of tissue consisted of a fibrous layer of variable thickness containing abundant small vessels and in one area plentiful foam cells sandwiched between the remains of a pigmented layer on one side and on the other portions of non pigmented epithelium of erratic distribution

provide some evidence that this bilaterally symmetrical disease is due to an autosomal recessive gene although a dominant mutation is possible. The elder sister has already been briefly mentioned (Forrester 1963 Case 1 SB). The only other evidence we have found in the literature of heredity of a very similar syndrome is Franceschetti's sibship of two, the children of consanguineous parents (1956).

One similar case without evidence of heredity has been described by Magnus (1927) and cases of "retinal dysplasia without systemic anomalies" (see Reese & Straatsma 1958) may also have the same disease. It is unlikely that our cases represent an extremely severe form of "falciform retinal fold" (see Discussion).

Case Histories

Case 1 When this patient was originally reported in 1963 (Forrester) it was recorded that a retrolental white mass was seen in both eyes at the age of 3 months. At 18 months she may have been slightly retarded mentally with a small circumference of head. Frequent minor convulsions were occurring with hypsarrhythmic changes in the EEG and she was treated with phenobarbitone. By the following year her fits had gradually disappeared and the phenobarbitone was stopped.

At her present age of 10 years she has bilateral microphthalmos, very shallow anterior chambers and cornea showing bilateral degenerative opacities with a bird-shaped pattern. See Fig. 1. No perception of light is present in either eye. It is not possible to examine satisfactorily behind the level of the pupils; no examination under anaesthesia has been done because further information is unlikely to be obtained. Chromosome studies show a normal female karyotype 46 XX. A recent EEG at age 10 years by the same service as in the previous examination showed no epileptic activity at all and her school teachers now rate her intelligence as average. The child was not premature; labour was normal and no treatment with oxygen was given.

Case 2 The younger child, a boy aged 4 years, is the only sibling of the first case mentioned above. The pregnancy was full term. Chromosomes show a normal male karyotype 46 XY. A recent EEG is normal and his general and mental development seem normal apart from the ocular findings under anaesthesia described below.

Microphthalmos with corneal diameters

	Right eye	Left eye
Horizontal	10 mm	9.5 mm
Vertical	10 mm	9.5 mm
Schiotz tonometry	4.5 mm	4.5 mm

Very shallow anterior chambers in both eyes

The likeliest explanation is the inheritance of an autosomal recessive gene from each phenotypically normal parent but a possibility is that a dominant mutated gene has been acquired from one parent

One probable example of the same condition has been reported previously by Franceschetti (1956) a brother and sister children of first cousins with pseudo glioma. The pupillary areas of the boy who could just perceive a bright light were greyish and the left eye had a small squint at the age of ten months the corneae became more opaque but with variable density in different areas. Mentally he was normal. The girl showed the same appearances in the pupils with a bluish tinge on the right side the right eye was abnormally large and dark brown while the left was abnormally small with a more grey tinge. Later in both children *seclusio pupillae* *iris bombe* and keratic precipitates developed but these inflammatory signs presumably have resulted from a developmental abnormality. Since the father seems to have been normal Norrie's disease would not account for this entity (it is worth considering since the parents are consanguineous that could explain an affected female child if the father had been affected). If Franceschetti's and our cases do suffer from the same disease the consanguinity of the parents of his cases supports our suggestion that an autosomal recessive gene has caused the disease in our cases.

We would interpret Magnus's case (1971) of probably bilateral total retinal detachments with persistent hyaloid artery in microphthalmic eyes as resembling our cases closely rather than being an example of bilateral hyperplastic primary vitreous as Babel (1966) has suggested.

Three possibly similar cases have been described by Clarke in 1898 but we consider that they are more likely in fact to be cases of Norrie's disease (see below). The father and mother were first cousins and the father was blind but had had operations for cataract in childhood signs of right cataract and left rotatory nystagmus were present in adult life. Numbers 1 (♂) 4 (♀) and 6 (♀) of the six children had opaque masses in the vitreous with retinal detachments the right eye of the first child was removed and showed an extensive retinal detachment and an opacity behind the lens. The fourth child was backward. No mention was made of family history in previous generations so that no final decision between Norrie's disease (mother assumed to be a carrier hence female children affected) and cases of recessively inherited retinal detachment as presumed in the sibship described in this paper can be made.

Two other possibilities should also be mentioned. Our cases could represent examples of the severe end of the spectrum of falciform fold of retina or be examples of retinal dysplasia without systemic involvement (see below in appropriate sections).



Fig 2

Case 2 Boy aged 4 years **Left eye** Very difficult to examine and photograph Small eyeball and shallow anterior chamber Irregular pupil with dense white opacity on iris infero temporally Through the crystalline lens white mass occupying anterior vitreous can be seen

Family history These are the only two children of non consanguineous parents who are entirely healthy and have no ocular abnormalities As far as she knows all the mother's three sisters and four brothers are normal her 11 nephews and nieces are all normal and her five cousins are normal She had no illnesses during either pregnancy As far as he knows all the father's three brothers and three sisters are normal his five neices and nephews are normal and his 20 cousins are normal All four grand parents were normal It was not practicable for us to examine these relatives

DISCUSSION

It seems likely that an inherited non attachment of retina exists in this brother and sister However since the retina is so well developed a detachment may have occurred in intrauterine life following a period of normal development

The likeliest explanation is the inheritance of an autosomal recessive gene from each phenotypically normal parent but a possibility is that a dominant mutated gene has been acquired from one parent

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(The term pseudo glioma has been used only once in this paper in quotation. A plea is made for ceasing to use this obfuscating term – nowadays even clinical examination can usually suggest a more accurate diagnosis)

Differential Diagnosis

Babel (1966) has given a useful account of the differential diagnosis of white masses behind the lens similarly Warburg (1966) from the point of view of differentiation of Norrie's disease

Retinal dysplasia (probably identical with 13-15 trisomy below as Hunter & Zimmerman 1965 suggested) In our two cases described here the absence of cerebral agenesis pulmonary stenosis and patent ductus cleft palate polydactyly/syndactyly polycystic kidneys and pancreatic cystic fibrosis *probably* but not absolutely necessarily excludes "retinal dysplasia" described by Reese & Blodi (1950) and Reese & Straatsma (1958). See also Krause (1946). Since many of the cases described by Reese & Straatsma probably would now be diagnosed as Bartholin Patau syndrome (Hunter & Zimmerman 1965) retinal dysplasia may not be a clinical entity. Twenty seven out of 44 of Reese & Straatsma's cases had only ocular disease however so they must have been similar to the two siblings we describe here. Only two affected sibships occurred in their whole series however one with three and one with two members but all except one (in the two member sibship) had multiple anomalies and that one had mental retardation. The eye condition is clinically similar – poor visual acuity enophthalmos microphthalmos (sometimes buphthalmos or normal size globe) ptosis retrolental masses retinal atrophy and gliosis recurrent vitreous haemorrhages and iridocyclitis with cataract and secondary glaucoma. Pathologically Reese & Straatsma's cases (1958) showed rosette formation disorganised cellular pattern with immature cells and gliosis in contrast to the findings in our case.

Falciform fold of retina The two patients described in our paper do not have falciform folds. However in the families described with the recessively inherited and often bilateral condition falciform retinal fold some cases occur of congenital total retinal detachment which made Weve (1936 and 1938) suggest the retiological identity of the two conditions (1938). We have not been able to examine the relatives of our two cases except for the mother and father who were normal so we cannot confidently state that falciform folds did not occur in all relatives. See also Mann (1935) and Joannides & Protonotarios (1965).

Persistent hyperplastic primary vitreous (Reese 1955) A generally accepted criterion of this diagnosis is that it is unilateral (with two exceptions one cited by Babel 1966 viz Magnus 1927 but we would prefer to interpret this case as resembling the ones we describe in the present paper. The other is mentioned by Jensen (1968) in his histopathological study of 13 cases - 14 eyes). Because of that if any bilateral cases did occur they would often probably be misdiagnosed and placed in one of the other groups discussed in this paper. Retinal detachment is unusual in PHPV.

Norrie's disease Since one of the affected children is a female with a normal karyotype since the father is normal and the parents are not consanguineous it seems very unlikely that their disease is Norrie's disease i.e. an X linked hereditary retinal detachment often with mental deficiency (Ash 1922 Heine 1975 Norrie 1971 R Wilson 1936 W M G Wilson 1949 Dahlberg Parrow 1956 Forssman 1960 Waardenburg et al 1963 Warburg 1966 and Hausen 1969). As Babel (1966) suggests the patients described by Sorsby et al (1951) probably had vitreo retinal degeneration.

Bartholin Patau syndrome Since no 13-15 trisomy and no systemic abnormalities such as hare lip cleft palate encephalocele meningocele malformations of heart lungs U G system and skeleton (e.g. six fingers) were present the diagnosis of the Bartholin Patau syndrome is excluded. In their paper on 13-15 trisomy Cogan & Kuwabara (1964) examined 25 control cases of microphthalmia or retinal dysplasia not related to trisomy and mention that some were bilateral but no details were given.

Dysplasia spondylo epiphysaria congenita The absence of any evidence of high myopia preceding the detachments and of skeletal abnormalities and of deafness excludes this condition (Roaf et al 1967 and Fraser et al 1969).

Similarly the absence of osteoporosis lax ligaments and muscular hypotony excludes the new syndrome described in three affected females out of a total of seven siblings by Saraux et al (1967) although clinically the conditions of the eyes (resembling a foetal uveitis) is rather similar.

Incontinentia pigmenti seems very unlikely because of the absence of abnormalities of skin colour and other stigmata and because a male is affected. See Warburg 1966.

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PERSISTENT HYPERPLASTIC PRIMARY VITREOUS IN NON-IDENTICAL TWINS

BY

M K WANG and C I PHILLIPS

Non identical twin females presented because one had a spontaneous left hyphaema. When this cleared a retrolental vascularised white mass presumably persistent hyperplastic primary vitreous (PHPV) was seen in the left eye. This eye was very slightly smaller than the right. The parents had noticed that her twin had a left convergent squint. The diagnosis of PHPV was also made in this twin's left eye which was also smaller than the right. An older male sibling is normal. The parents are not consanguineous.

A recessive gene is the likeliest explanation but an intra uterine environmental factor such as infection is a definite possibility. (No other sibships with or cases of persistent hyperplastic primary vitreous with affected first degree relatives seem to have been reported.)

Key words: vitreous - malformations - heredity - twins

Persistent hyperplastic primary vitreous (PHPV) is characterised by the usually unilateral presence of a retrolental opaque tissue in a microphthalmic eye. The anterior chamber usually is shallow and the irido corneal angle is often incom-

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pletely developed. The dense fibrovascular tissue which forms behind the lens extends laterally to the equator and elongated ciliary processes are usually visible. Remnants of the hyaloid artery are present within this tissue near the posterior pole of the lens (Reese 1955, Manshott 1958, Hogan & Zimmerman 1967).

Report of Cases

Case 1 A fourteen month old girl (birth weight 3910 g) was admitted with a diffuse left hyphaema which appeared at an episode of crying. There was no history of injury. The left cornea was clear and the eye was white. In six weeks time the anterior chamber became macroscopically clear.

As no red reflex was then seen in the left eye an examination under anaesthesia was done. The left eye seemed smaller than the right and its horizontal corneal diameter was 11.5 mm whereas the right cornea was 12 mm by measurement with calipers. The left anterior chamber was shallow but the iris was normal. Behind the left lens was a total white mass with large surface vessels; the mass was more dense in the centre than in the periphery. Temporally and inferiorly were seen drawn out ciliary processes. The right eye was normal but subsequently at the age of 2 1/2 years -8D of myopia has been found.

Case 2 The parents mentioned that the left eye of the twin sister of the presenting patient (case 1) occasionally turned inwards. On examination this twin (birth weight 3949 g) also showed no red reflex in the left eye. Under anaesthesia the right eye was found to be normal but the left eye was microphthalmic. The right horizontal corneal diameter was 12 mm and the left 11.5 mm by calipers. Through a clear cornea the left anterior chamber was of normal depth. The iris showed no abnormalities. The infero-nasal edge of the lens was visible through the dilated pupil but the lens was not obviously tilted. There were some sparse opacities of the anterior capsule but the rest of the lens appeared clear. Behind the lens was a vascularised white mass. There was scattered pigment on the surface, some of which was elongated into strands. The vessels appeared to radiate from the centre outwards. The centre of the mass was denser than the periphery. Although no definite drawn out ciliary processes were seen it was thought that the pigment strands might be the processes. There was no defect on transillumination. The right eye is still normal on examination at the age of 2 1/2 years and is emmetropic.

While the patients were under anaesthesia blood was taken for genotyping. The results showed that the twins were not identical. The genotype of the hyphaema twin was $A_1 M_s N_{s_1} CDe/cDe (R_1 R)$. The other's genotype was $A_1 N_s N_{s_1} CDe/cDe (R_1 +)$.

Further questioning of the mother of the twins revealed that there had been a threatened abortion at ten weeks of pregnancy. The twins were delivered at 37 weeks gestation. No drugs were taken during the pregnancy but oxygen was administered to the hyphaema twin for twenty four hours.

Both parents and a four year old brother were examined but no ocular abnormalities were found. The parents are not consanguineous and they were not aware of any relevant ocular family history.

Discussion

Persistent hyperplastic primary vitreous is the unilateral presence of a retrolental opaque tissue in a microphthalmic eye. Although this congenital condition had been given other descriptive names it was Reese in the Jackson lecture of 1955 who made a strong case for the present terminology of PHPV. The affected eye of each of these twins was microphthalmic although in one it was only after close comparison that this was realised. The fact that the condition is unilateral must very probably exclude retrolental fibroplasia in spite of oxygen being administered to one child (in any case only a short administration was given).

It has been suggested that if unilaterality is accepted as a criterion of PHPV any bilateral cases which might occur would be misdiagnosed as, for example, congenital non attachment of retina, a variant of falciform retinal fold, retinal dysplasia, etc. (Phillips et al 1972). Conversely there might exist patients who appear to have unilateral PHPV who may in fact have some other disease e.g. unilateral examples of congenital non attachment of retina, falciform retinal fold or a variant retinal dysplasia, etc. We would admit that the siblings described here could be examples of this latter mistake especially as hereditary cases of PHPV seem to be very rare.

The majority of patients with PHPV present because of a white reflex showing through the pupil. Indeed the condition is an important differential diagnosis of so called 'pseudoglioma' (see Sanders 1952, Babel 1966, Warburg 1966). Most of the conditions which a pseudoglioma may turn out to be can present with a spontaneous hyphaema (Howard 1962) as did our first case.

Jensen (1966) in his histopathological study found PHPV bilaterally in one case of a series of thirteen patients. Babel (1966) cites Magnus (1921) as describing a bilateral case although we would suggest that this case may well be one of bilateral non attachment of retina (Phillips et al 1972). The fact that the vast majority of cases are unilateral does not suggest a hereditary cause and we have found no record of hereditary cases - excluding the eight cases in three families of bilateral persistent hyaloid artery cited by Waardenburg et al (1966) and also cases of falciform fold of retina. Also there appear to be no recorded cases of PHPV in twins.

The twins who are presented in this paper are non identical as shown by genotype studies. A circulating toxin of some sort might have caused the condition but all four eyes should have been affected. Trauma of some type may be a possibility but a transplacental infection is more likely. Whatever the cause it may have preceded the threatened abortion at ten weeks pregnancy.

Since no reports of hereditary cases of persistent hyperplastic primary vitreous have been previously reported we have some reservations in claiming these twins as examples implying a recessive inheritance. From this point of view a non twin sibship would have been more cogent evidence — a simultaneous environmental noxious influence *in utero* in our cases cannot be ruled out.

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TRANSLUCENCY OF THE SCLERA

I Localized Preplaque-Translucency

BY

M S NORN

Gross examination with a pencil torch of 319 non selected patients disclosed in 117 cases a greyish translucent streak in the sclera along the tendon attachment of one or more of the horizontal eye muscles

The phenomenon was found to rise in frequency with increasing age having been noticed in only 4 per cent of the patients aged under 60 against in 30 per cent of those aged 60-69 43 per cent aged 70-79 and 54 per cent aged ≥ 80

Such streaks were most often seen over the areas of the medial muscles

The phenomenon bears no relation to the occurrence of pinguecula white girdle or development of inverse astigmatism

The phenomenon is presumably a precursor of scleral plaques

Key words: localized - scleral translucency scleral plaques - preplaques

Simple examination of the sclera with an ordinary electric torch (pencil torch) without magnification will often disclose a localized slate grey streak present just in front of the insertion of a medial or a lateral rectus

The band is not recognizable in the slit lamp where in other words the

sclera apparently is perfectly normal like the surrounding white sclera. In direct slit lamp light or weak light will again render the greyish discoloration just visible but this is best recognized by gross examination with a pencil torch without using the slit lamp.

The phenomenon is comparable to that of scleral scatter where beginning corneal oedema is best recognized by concentrating a strong light on the limbus corneae and subjecting the rest of the cornea to gross examination. The cornea though apparently clear in the slit lamp will then become cloudy milky white.

The phenomenon under review is the reverse gross examination discloses a translucent region in an apparently opaque white sclera.

The phenomenon localized translucency of the sclera seems not to have been described before.

It is far more frequent than another phenomenon described in the literature under different names: scleral plaques, hyaline scleral plaques, transparency or translucency of the sclera, superficial deficiency of the sclera and Schleralverdunnung (Cogan 1959, Boshoff 1942, Graves 1941, Roper 1945).

A scleral plaque manifests itself by a local transparency of the sclera allowing the uveal tissue to show through the sclera. Unlike the localized scleral translucency the transparent region of a scleral plaque is sharply demarcated from the surrounding normal sclera and the phenomenon is best observed in slit lamp light under magnification. Such plaques may be so small as to be only recognizable by examination in the slit lamp.

I have only noticed scleral plaques in regions where gross examination with a pencil torch also revealed localized translucency round the plaque.

The localized translucency described in this paper may possibly be a precursor of scleral plaques. I have therefore termed the phenomenon 'localized preplaque translucency'.

Plaques and preplaques bear no relation to the disorder termed *scleromalacia perforans* occurring in patients suffering from rheumatoid arthritis and from porphyria. In scleromalacia the eyeball may become perforated. Plaques on the other hand seem to be quite harmless.

Deposits in and above the sclera (ochronosis, argyrosis, adrenalin melanosis) rarely cause differential diagnostic problems and translucent scleral areas round emissary nerves and veins are so small as to be easily distinguishable from plaques.

In sclerectasia the bulging effects thinning of the sclera while in staphyloma uveal tissue with pigment is included in the process.

Plaques and preplaques on the other hand presumably consist of translucent sclera of normal thickness. The translucent scleral region is at least on its ex-

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M S NORN

Gross examination with a pencil torch of 319 non selected patients disclosed in 11/ cases a greyish translucent streak in the sclera along the tendon attachment of one or more of the horizontal eye muscles.

The phenomenon was found to rise in frequency with increasing age having been noticed in only 4 per cent of the patients aged under 60 against in 30 per cent of those aged 60-69 43 per cent aged 70-79 and 54 per cent aged ≥ 80 .

Such streaks were most often seen over the arcs of the medial muscles.

The phenomenon bears no relation to the occurrence of pinguecula white girdle or development of inverse astigmatism.

The phenomenon is presumably a precursor of scleral plaques.

Key words: localized - scleral translucency scleral plaques - preplaques

Simple examination of the sclera with an ordinary electric torch (pencil torch) without magnification will often disclose a localized slate grey streak present just in front of the insertion of a medial or a lateral rectus.

The band is not recognizable in the slit lamp where in other words the

Table I
Site of scleral preplaque translucency (117 cases)

Over the area of	Number in per cent
One medial rectus	11
Two medial recti	41
Two lateral recti	5
One med rect plus one lat rect	1
Two med rect plus one lat rect	8
One med rect plus two lat rect	3
Two med rect plus two lat rect	31
Total	100

liathermy of retinal detachment. The youngest person with no extrinsic cause was 47 years old. The incidence of translucency was seen to rise gradually with increasing age. Of the patients aged under 60, no more than 4 per cent presented localized translucency, against 30 per cent of those aged 60-69 (statistically significant difference $P < 0.001$), 43 per cent of those aged 70-79 and 54 per cent of those aged ≥ 80 .

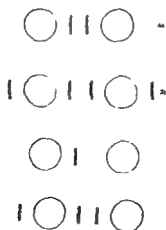


Fig. 1

Most frequent sites of preplaque translucency (see in addition Table I)

ternal surface on a level with the surrounding normal sclera assessed in the slit lamp

The object of the present paper has been to describe the localized preplaque translucency, while the incidence of scleral plaques will be dealt with in a future paper

Method and Material

Each patient's eyes were subjected to gross examination with a pencil torch the sclera having been examined systematically with the patient looking to the right to the left upwards and downwards. Grey areas were marked on a diagram. Then followed similar examination in the slit lamp for occurrence of scleral plaques.

By localized preplaques we understand regions in which on gross examination the uveal tissue shows through the sclera within a local area. Eyes displaying diffuse translucency of the whole sclera or of the whole limbal circumference were not included.

The investigation comprised a total of 319 non selected patients of whom some were from my own consultation (Vanløse) and the others from the Out Patient Eye Department Kommunchospitalet. Table II shows the age incidence.

Result

The localized preplaque translucency was where present seen within the region just in front of the insertion of a horizontal rectus muscle. The grey area constituted in all cases a vertical about 1 mm broad streak along the entire width of the tendon attachment.

Translucency was in no instance demonstrated in relation to the vertical muscles. Uncharacteristic sites were shown in three cases only: all pathological (translucency following episcleritis and following surgical diathermy in cases of retinal detachment where the treated region became translucent).

Preplaque translucency was noticed in 117 patients. It was most often seen over the area of a medial rectus. In 31 per cent of the cases it was present in front of all four horizontal muscles. The sites are shown in Table I and Fig. 1.

The incidence of preplaques rises with increasing age (Fig. 2). Preplaques are absent in individuals below the age of 30. The youngest patient with translucency was a woman aged 31 in whom the phenomenon was due to surgical

Table III

Relation between scleral preplaques pinguecula white girdle and inverse astigmatism in per cent (319 patients)

	Pinguecula	Girdle	Astigmatism	Number
Preplaque alone	37.6	18.8	22.4	85
Plaque and preplaque	21.9	21.9	15.6	32
Neither plaque nor Preplaque	40.5	59.8	63.9	202

In the whole series there were found on an average 2.6 translucent regions among the individuals with translucency

No sex difference was detectable

Of the total series 37 per cent had preplaques while 11 per cent at the same time had proper scleral plaques. Cases of plaques among individuals with preplaques were seen to rise in number with increasing age (plaques present in 9 per cent with preplaques aged under 40 against 24 per cent aged 40 and 48 per cent aged 80)

The incidences of preplaques and plaques have been compared with those of three other phenomena which likewise rise in number with increasing age. These are pinguecula white girdle of Vogt on the cornea in the limbal region and development of inverse astigmatism (Tables II and III)

No correlation was demonstrated between preplaques or plaques and the above phenomena

Discussion

The phenomenon described above called preplaques occurs more frequently than the well known scleral plaques. The sites incidence and age distribution go to show that the scleral plaques develop from preplaques.

The following may be a typical development with increasing age: first one preplaque in front of one of the medial recti then another in front of the other medial rectus and then yet another preplaque in front of a lateral horizontal muscle or a proper scleral plaque develops within one of the previously developed preplaques.

The origins of preplaques and plaques are obscure. In the series under

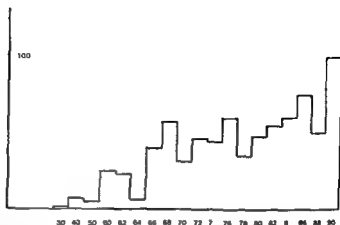


Fig 2

Incidence of scleral preplaque translucency in different age groups (a total of 319 examined) *Abscissa* age in part in two year groups *Ordinate* Percentage number of individuals with preplaques within the age group concerned

The number of muscles with translucency in front likewise rises with increasing age in the patients aged under 60 the sites with translucency averaged 1.5 in those 60-69 years old 2.4 70-79 years old 2.6 80-89 years old 2.9 and in those ≥ 90 years old the average was 3.3

In other words fairly young individuals were seen to have only one translucent region e.g. over the area of a medial rectus while the age group of 80-90 have on an average three transparent regions e.g. over the areas of two medial recti and one lateral rectus

Table II

Age distribution of patients with scleral preplaque translucency pinguecula white girdle and inverse astigmatism in per cent (319 patients)

Age	Preplaque	Pinguecula	Girdle	Astigmatism	Number
< 60	4	11	11	2	53
60-69	30	41	15	18	66
70-79	43	29	20	24	136
80-89	54	39	25	19	61
≥ 90	100	33	100	100	3
Total	37	31	19	17	319

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A FAMILY PEDIGREE WITH CORNEAL DYSTROPHY TAPETORETINAL DEGENERATION AND ALBINISM

BY

A PINCKERS A J OTTO and J E A VAN DEN HEUVEL

This paper describes a family in which three abnormal eye conditions were observed

- a) a dominant autosomal corneal dystrophy which might be interpreted as an incompletely developed granular corneal dystrophy (Groenouw I)
- b) a recessive autosomal diffuse tapetoretinal degeneration
- c) an intermediately transmitted albinism

Also the detailed examination of a female patient with corneal dystrophy and tapetoretinal degeneration who revealed signs of segmental demyelination and remyelination possibly a recessing neuropathy the presence of mucopolysaccharidoses was not demonstrable in a biopsy specimen from the sural nerve

Key words: corneal dystrophy - tapetoretinal degeneration - albinism - heredity

In 1969 we examined a boy with albinism in whose father we found translucency of the iris corneal dystrophy and tapetoretinal degeneration the examination was repeated after 3 years

Stimulated by a publication on the combined inheritance of nodular corneal dystrophy and retinitis pigmentosa both linked to the colour of the iris (Nizetic & Sakic 1967) we decided to carry out an exhaustive study on the family Our purpose was to establish whether the symptoms observed are jointly inherited or a combination of different hereditary conditions

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review a likely explanation of the occurrence of preplaques could be given in no more than three out of 117 cases. In one of these the phenomenon occurred following episcleritis and in the two others after surgical diathermy in cases of retinal detachment.

A preplaque might be conceived to represent a hyaline degeneration. However, preplaques are not particularly frequent among patients with pinquecula which is a hyaline degeneration.

The white girdle of Vogt consists of calcareous deposits within the limbal region, presumably due to evaporation in this exposed region. No correlation exists between white girdle and preplaques.

Inverse astigmatism developed in elderly individuals is possibly due to traction of the horizontal muscles on the eyeball. No correlation exists between inverse astigmatism and preplaques.

The phenomena studied thus do not contribute towards elucidating the cause of the preplaque translucency in the sclera.

The scleral plaques will be dealt with in greater detail in a future paper.

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Material

The entire family study was completed within a period of 6 months during which period some members were examined on several occasions. Data on family members who had emigrated were obtained with the kind collaboration of ophthalmologists abroad. Later on a fortunate coincidence enabled us to examine two of these family members in person.

Methods

The routine examination of all these patients included determination of the visual acuity, slit lamp examination of the refractive media and funduscopy dependent on the findings obtained and time available. Supplementary examinations included visual field determinations, electroretinography (ERG), electro-oculography (EOG), determination of the dark adaptation curve according to the method of Goldman-Weekers and colour vision tests. Translucency of the iris if any was present was assessed with the help of a slit lamp.

The examination of one female patient included a study of the blood biochemistry and a detailed neurological examination.

The results of the colour vision tests were coded following the classification of François & Verriest (1957). The EOG was recorded in the way described by Pinckers & Thijssen (1971) and the ERG by the method described by Pinckers (1971).

Results

Fig. 1 shows the pedigree of the family studied. For convenience the findings on albinism are presented in a separate pedigree (Fig. 5).

The case histories of the original household are presented in detail; the findings obtained together with the data regarding the remaining family are presented in Tables I and II.

Case VI 21: a female born in 1933. At age 36: VODS cyl +0.25 axis 90° = 1.0; translucency of the iris; cornea and lens clear. Fundi: fine to coarsely granular pigment at the right macula; the periphery of the pigment epithelium shows a coarsely granular aspect. ODS with a mottled and streaked distribution of pigment. Normal ERG, subnormal EOG, ratio OD 17.4 and OS 16. Normal colour vision. Blond (not white) hair.

Clinical features are unchanged 3 years later. Normal EOG and normal colour vision. ERG responses after 12 minutes dark adaptation slightly diminished.

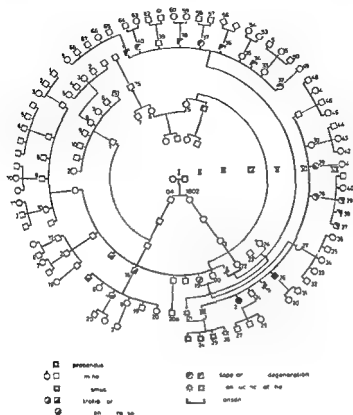


Fig 1

Ped gree of a fam ly with corneal dystrophy tapetoretinal degeneration and albinism

Case VI 93 male born 1931 At age 37 VOD cyl -1.0 axis $80^\circ = 0.3$ VOS 0.6 em metropic alternating divergent strabismus photophobia translucency of the iris the right cornea shows two small subepithelial spots while the left cornea shows a larger subepithelial spot having the appearance of a grain of sugar corneal sensitivity normal no corneal vascularization lenses clear Fundi a) oval and sharply defined areas of macular degeneration having a red orange colour b) a normal appearance of the optic discs and vessels c) atypical pigment degeneration at the retinal periphery (atypical because pigment changes of the trabecular structures are absent) The ERG is gravely disturbed maximum obtainable a wave amplitude $20 \mu V$ that of b wave $30 \mu V$ FFF 4/second EOG ratio OD 165 and OS 179 The dark adaptation curve shows diminution of both adaptation segments Colour vision is seriously disturbed with no clearly demonstrable axis direction

Table I
Survey of findings in patients with corneal dystrophy

Pat no	Sex	Date of birth	VOD	VOS	Colour vision	Dark adaptation
V-15	M	1903	10	10	-	no
V-16	M	1909	10	10	-	no
V-21	M	1898	10	10	-	no
VI-15	M	1944	10	10	-	-
VI-17	F	1939	10	10	-	-
VI-22	M	1931	03	06	seriously disturbed	disturbed
VI-23	F	1938	03	03	seriously disturbed	disturbed
VI-25	M	1940	10	10	-	cone segment slightly diminished
VI-26	M	1942	08	12	slightly disturbed	disturbed
VI-28	F	1928	08	08	-	-
VI-32	F	1936	10	10	-	no
VI-34	M	1945	10	002	-	no
VI-36	M	1941	10	10	-	no
VI-37	F	1937	08	08	-	no
VI-38	M	1938	10	10	-	no
VI-40	F	1931	10	10	-	no
VI-41	M	1932	10	10	-	no
VII-37	M	± 53	10	10	-	-
VII-38	M	± 57	10	10	-	-
VII-39	M	± 59	10	10	-	-

Clinical features are virtually unchanged 3 years later. The ERG is extinguished apart from an FFT of 20/second (Fig 2). Pathological EOG ratio OD 112 and OS 115 (Fig 3). Dark adaptation curve increasingly disturbed.

Case VII 23 male born 1957 (proband) At age of 12 VOD sph +0.5 cyl +4 axis 95° = 0.3 VOS cyl +4 axis 85° = 0.5 convergent strabismus OD nystagmus translucency of the iris cornea and lenses clear Fundi albinotic features with hypoplasia of both maculae no abnormal pigmentation White hair Normal FPG Colour vision slightly disturbed with no clearly demonstrable axis direction.

Clinical features are unchanged 3 years later no significant change in the FPG. Dark adaptation curve attains a normal level of adaptation. Colour vision AOHR normal panel 1//DT.

Case VII 24 male born 1962 At age 1 VOD sph -4.0 cyl +3 axis 100° = 0.30 VOS cyl +3 axis 80° = 0.4 alternating convergent strabismus nystagmus translucency of the iris cornea and lenses clear Fundi albinism with macular hypoplasia Normal ERG White hair.

Table 1 (cont)

EOG	ERG	Other findings
no	—	presbyopia
—	—	presbyopia
no	—	presbyopia posterior embryonic axial cataract
—	—	none
—	—	none
disturbed	almost extinguished	tapetoret transluc of iris
—	extinguished	tapetoret degen
no	—	left fundus 1 pigment clump
disturbed	severe scotopic and photopic disturbance	tapetoret degen
—	—	none
no	—	none
no	—	cataract posterior pole OS
—	—	none
—	—	anterior embryonic axial cataract
—	—	none
—	—	none
—	—	none
—	—	none
—	—	none

Clinical features are unchanged 3 years later Dark adaptation curve ERG and colour vision (AOHRR 100 Hmn test) normal

Case V II ♀ mal born 1960 At age 9 VOD sph +3 cyl +1.25 axis 95° - 1.0 VOS sph 3.5 cyl +5.0 axis 90 = 0.1 convergent strabismus OS no nystagmus translucency of the iris clear corneae both lenses show very thin radiating opacities at the anterior cortex and a thin oval opacity at the posterior capsules Fundi very little pigment present but decidedly more than in VII 93 maculae not hypoplastic ERG and colour vision normal White hair

Clinical features are unchanged 3 years later Normal ERG EOG AOHRR test panel D 15 test and dark adaptation curve

Case V II ■ female born 1967 At age 4½ VOD +2 = 1.0 VOS +2 = 0.5 alternating convergent strabismus Translucency of the iris ginger hair Fundi foveolar reflex absent both posterior poles strewn with finely to coarsely granular pigmentation no areas of depigmentation in this area retina outside the areas of the posterior poles very poorly pigmented

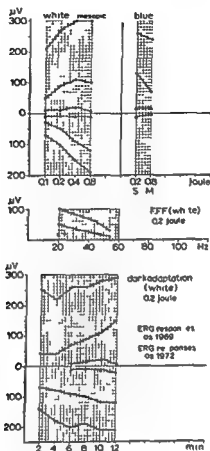


Fig 2

Electroretinogram of patient No. VI 22. The lines connecting the filled circles represent the normal range of electroretinographic responses.

Case VI 23 female born 1938 At age 32 VOD 0.3 after correction sph +1.0 cyl +0.5 axis 115° VOS 0.3 after correction sph +1.0 cyl +0.5 axis 90° TOD 12 mmHg TOS 11 mmHg. No translucency of the iris. Both corneae show marked dystrophy: candle grease spots, sugar crystals, and thin lines of subepithelial localization with only a few small spots deeper in the stroma (Fig 4). Normal corneal sensitivity, no corneal vascularization. Fundi: sharply defined oval red-orange macular degeneration discs and vessels of normal appearance, large clumps of pigment visible in the retinal periphery as well as a few trabeculae and scattered areas of unmistakable choroidal atrophy. Peripheral visual fields: pericentral annular defects. ERG: extinguished. Colour vision: seriously disturbed. Ishihara 1/100 Hue OD (CI 19° type \ \ 100 Hue OS CI = 613 type \ \.

Clinical features hardly changed 2 years later. ERG: extinguished. Dark adaptation curve: disturbed for both segments. Panel D 15 OD 3 ML OS C T+ ret \ \.

Blood biochemistry: haemoglobin 9.2 mmole/l, haematocrit 0.41, serum iron 7 mmole/l, iron binding capacity 66 mmol/l. Liver and kidney functions: undisturbed.

Pat n	Sex	Year of birth	VOD	VOS	Findings	Special examination
VI-1	M	1889	07	06	Cortical cataract	
V-8	F	1915	10	10	Cornea guttata	
V-19	F	1895	00	00	Myop a gravis cpi and endothelial dystrophy aphakia	DA no
V-14	M	1897	015	10	Postherpetic iridal atrophy corneal macula	DA no
V-20	M	1900	07	10	Iris hypopygia pterygium transclucency of iris	
V-2	F	1903	10	10	Hypermetropia presbyopia	
V-23	M	1906	10	10	Poorly pigmented fundus with scattered granular pigment	
V-24	F	1908	10	10	Normal	
V-5	M	1910	10	10	Thyrogenic exophthalmos	
VI-6	M	1919	10	10	Choroidal nevus presbyopia	
VI-7	M	1931	10	10	Normal	
VI-8	M	1937	03	10	Amblyopia	
VI-9	M	1934	10	10	Normal	
VI-10	F	1936	10	10	Normal	
VI-12	M	1926	10	10	Hypermetropia presbyopia	
VI-13	M	1909	10	10	Lapoid arcus presbyopia	
VI-14	M	1930	10	10	Normal	
VI-16	F	1945	10	10	Anisocoria	
VI-18	F	1943	10	10	I depigmentation equator of the fundus OD	
VI-19	M	1948	10	10	Normal	
VI-20	F	1951	10	10	Normal	
VI-20a	M	1934	10	10	Hypermetropia	
VI-21	F	1933	10	10	Translucency of iris pigment changes in fundus	
VI-24	M	1931	10	10	Slight cortical cataract	

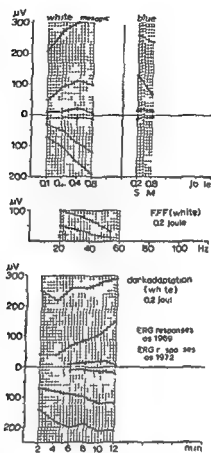


Fig 2

Electretinogram of patient No VI 22 The lines connecting the filled circles represent the normal range of electretinographic responses

Case VI 93 female born 1938 At age 32 VOD 0.3 after correction sph +1.0 cyl +0.15 axis 115° VOS 0.3 after correction sph +1.0 cyl +0.75 axis 30 TOD 12 mmHg TOS 11 mmHg No translucency of the iris Both corneae show marked dystrophy candle grease spots sugar crystals and thin lines of subepithelial localization with only a few small spots deeper in the stroma (Fig 4) normal corneal sensitivity no corneal vascularization Fundi sharply defined oval red orange macular degeneration discs and vessels of normal appearance large clumps of pigment visible in the retinal periphery as well as a few trabeculae and scattered areas of unmistakable choroidal atrophy Peripheral visual fields pericentral annular defects ERC extinguished colour vision seriously disturbed Ishihara I 100 Hue OD CI 19° type \\\ 100 Hue OS CI = 613 type \\\

Clinical features hardly changed 2 years later ERG extinguished dark adaptation curve disturbed for both segments Panel D 15 OD 3 ME OS C T+ ret \\\

Blood biochemistry haemoglobin 9.2 mmole/l haematocrit 0.11 serum iron 2.1 mmole/l iron binding capacity 66 mmol/l Liver and kidney functions undisturbed

VII-31	I	1961	10	10	Normal
VII-33	I	1961	10	10	Myopia astigmatism
VII-35	M	1961	10	10	Hypermetropia
VII-40	I	1961	10	10	Normal
VII-41	M	1961	06	06	Normal
VII-45	I	1961	10	10	Hypermetropia
VII-46	M	1961	10	10	Hypermetropia
VII-47	F	1961	10	10	Hypermetropia
VII-48	M	1961	10	10	Hypermetropia
VII-49	M	1961	10	10	Normal
VII-50	M	1961	03	03	Persistent pupillary membrane OS
VII-51	I	1961	05	05	Abnormal OS anterior embryonic axial cataract ODS
VII-52	M	1961	10	10	Normal
VII-53	F	1961	10	10	Normal
VII-54	F	1961	10	10	Normal
VII-55	?	?	-	-	Malignant osteopetrosis
VII-56	?	?	-	-	Malignant osteopetrosis
VII-57	I	1961	10	10	Incipient corneal dystrophy OS?
VII-58	I	1961	10	10	Normal

VI-21a	M	1961	10	10	Translucent iris pigment changes in fundus
VI-21b	I	1961	10	10	Normal
VI-21c	M	1961	10	10	Normal
VI-21d	F	1961	10	10	Translucent iris pigmented changes in fundus
VI-21e	M	1961	10	10	Translucent iris
VI-21f	F	1961	10	10	Normal
VI-21g	I	1961	10	10	Hypermetropia
VII-21a	M	1961	01	01	Translucent iris rotator/nystagmus pigment changes in fundus
VII-21b	I	1961	10	10	Translucent iris pigment changes in fundus converg strabismus
VII-21c	M	1961	03	03	Convergent strab hypermetropia astigmatism
VII-21d	F	1961	-	-	Translucent iris pigment changes in fundus converg strabismus
VII-21e	I	1961	-	-	No nystagmus

Table II (cont.)

Pat no	Sex	Year of birth	VOD	VOS	Findings	Special examination
VI-27	F	1930	1.0	1.0	Normal	EOG disturbed DA disturbed Diminished cone adaptation LOG no
VI-29	F	1943	0.6	0.5	Tapetoretinal degeneration	
VI-30	F	1935	1.0	1.0	Astigmatism	
VI-33	F	1942	1.0	1.0	Astigmatism	
VI-35	F	1933	1.0	1.0	Myopia astigmatism	EOG + FRG + DA + Colour repeatedly no ERG + colour normal ERG subnormal
VI-39	M	1943	1.0	1.0	Normal	
VI-42	M	1934	1.0	1.0	Thyreogenic exophthalmos	
VII-15	F	1951	1.0	1.0	Normal	
VII-16	M	1955	1.0	1.0	Myopia	
VII-17	F	1960	1.0	1.0	Normal	
VII-18	M	1964	1.0	1.0	Normal	
VII-19	F	1967	1.0	1.0	Normal	
VII-23	M	1957	0.3	0.5	Ocular albinism	
VII-24	M	1962	0.3	0.4	Ocular albinism	
VII-25	M	1960	1.0	0.1	Poorly pigmented fundus	
					translucent iris	
VII-26	F	1967	1.0	0.5	Hypermetropia	
					translucent iris	
VII-27	M	1960	1.0	1.0	Pigment changes in fundus	
VI-28	M	1962	1.0	1.0	Pigment changes in fundus	
VII-29	F	1969	?	?	Normal	
VII-30	F	1946	1.0	1.0	Incipient corneal dystrophy OD?	

Case	Sex	Age	Ref	Findings	Diagnosis
VI-31	F	18	10	Normal	Normal
VI-34	F	18	10	Myopia 21 gm	Myopia
VI-35	M	18	10	Myopia 18 gm	Myopia
VI-40	F	18	10	Normal	Normal
VI-41	M	18	10	Hypermetropia	Hypermetropia
VI-45	F	19	10	Hypermetropia	Hypermetropia
VI-46	M	19	10	Hypermetropia	Hypermetropia
VI-47	F	19	10	Hypermetropia	Hypermetropia
VI-48	M	19	10	Normal	Normal
VI-49	M	19	10	Normal	Normal
VI-50	M	19	10	Normal	Normal
VI-51	F	19	10	Normal	Normal
VI-52	M	19	10	Normal	Normal
VI-53	F	19	10	Normal	Normal
VI-54	F	19	10	Normal	Normal
VI-55	F	19	10	Normal	Normal
VI-56	F	19	10	Normal	Normal
VI-57	F	19	10	Normal	Normal
VI-58	F	19	10	Normal	Normal
VI-59	F	19	10	Normal	Normal
VI-60	F	19	10	Normal	Normal
VI-61	F	19	10	Normal	Normal
VI-62	F	19	10	Normal	Normal
VI-63	F	19	10	Normal	Normal
VI-64	F	19	10	Normal	Normal
VI-65	F	19	10	Normal	Normal
VI-66	F	19	10	Normal	Normal
VI-67	F	19	10	Normal	Normal
VI-68	F	19	10	Normal	Normal
VI-69	F	19	10	Normal	Normal
VI-70	F	19	10	Normal	Normal
VI-71	F	19	10	Normal	Normal
VI-72	F	19	10	Normal	Normal
VI-73	F	19	10	Normal	Normal
VI-74	F	19	10	Normal	Normal
VI-75	F	19	10	Normal	Normal
VI-76	F	19	10	Normal	Normal
VI-77	F	19	10	Normal	Normal
VI-78	F	19	10	Normal	Normal
VI-79	F	19	10	Normal	Normal
VI-80	F	19	10	Normal	Normal
VI-81	F	19	10	Normal	Normal
VI-82	F	19	10	Normal	Normal
VI-83	F	19	10	Normal	Normal
VI-84	F	19	10	Normal	Normal
VI-85	F	19	10	Normal	Normal
VI-86	F	19	10	Normal	Normal
VI-87	F	19	10	Normal	Normal
VI-88	F	19	10	Normal	Normal
VI-89	F	19	10	Normal	Normal
VI-90	F	19	10	Normal	Normal
VI-91	F	19	10	Normal	Normal
VI-92	F	19	10	Normal	Normal
VI-93	F	19	10	Normal	Normal
VI-94	F	19	10	Normal	Normal
VI-95	F	19	10	Normal	Normal
VI-96	F	19	10	Normal	Normal
VI-97	F	19	10	Normal	Normal
VI-98	F	19	10	Normal	Normal
VI-99	F	19	10	Normal	Normal
VI-100	F	19	10	Normal	Normal

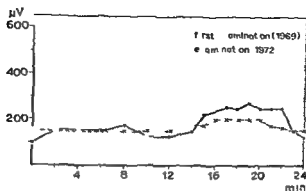


Fig 3
Electro-oculogram of patient No VI 22

Platelet count 248 000 bleeding time 1 57 clotting time 2 57 Fibrinogen 1 94 Cholesterol 6 6 mmole/l triglyceride 1 62 mmole/l Lipidogram α 26 8 % (normal 10-30) pre β 22 0 % (normal 16-36) β 51 2 % (normal 42-66)

Neurological examination hirsutism of the legs moustache contracted little fingers no other abnormalities apart from indifferent plantar reflexes EMG normal EEG diffusely disturbed

Biopsy from the sural nerve marked acid phosphatase activity in the Schwann cells possibly indicative of storage although this is not actually demonstrable No evident degeneration of the myelinated fibres but signs of segmented demyelination and remyelination The Haggqvist preparations show indications of a primary axonal affection or dying back neuropathy Acid phosphatase activity also in perineural space epineurial fibroblasts (particularly perivascular) and in the vascular walls possibly indicative of storage and/or phagocyte activity

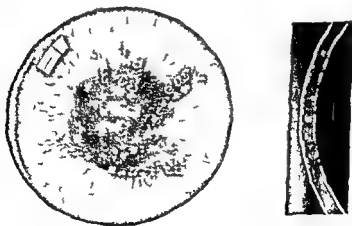


Fig 4
Artist drawing of corneal dystrophy patient No VI 23

The principal data with those on the other members of the family are summarized in Tables I and II. There may also be incipient corneal dystrophy in 2 patients who because this could not be established with certainty have not been included in Table I.

Case VI 30 female born 1966 At age II VODS 10 emmetropic small superficial opacity in lower temporal area of the right cornea otherwise normal features of the media and the ocular fundi.

Case VI 63 female born 1964 At age 7 VODS 10 emmetropic in the left cornea a subepithelial delicate brownish line extends from the bottom to the upper temporal area otherwise normal features of the media and the ocular fundi.

DISCUSSION

Corneal dystrophy was diagnosed in 20 patients. 2 patients may show an incipient dystrophy in 1 patient (V 19 female) corneal dystrophy was assumed to exist on genetic grounds and in view of the family history.

Tapetoretinal degeneration occurred in only 1 sibship in 4 of the 9 children it involved both the posterior pole and the peripheral retina.

Translucency of the iris (Fig. 5) was found in 15 patients but there were signs of complete albinism in only two patients.

It can be concluded from Figs. 1 and 5 that the three eye conditions were independently transmitted and coincided in case VI 22 the father of the proband. A separate discussion of the three affections seems justified. But there is one fact that should particularly be mentioned the family knows that nightblindness occurs only in the individuals with fair hair (VI 22 through VI 31) examination disclosed that indeed the tapetoretinal degeneration was confined to fair haired individuals and that the translucency of the iris was not linked to it. Linkage to the colour of the iris (Nizetić & Sakic 1951) was not demonstrable because all of the family members had blue irides. The combination of tapetoretinal degeneration with fair hair was therefore an actual reality a circumstance which we are quite unable to explain.

Corneal dystrophy

We may assume that the corneal dystrophy obeys autosomal dominant transmission the affection is transmitted from father to son from mother to daughter and from father to daughter moreover the offspring of individuals without a corneal dystrophy (e.g. V 13 and V 14) proved to remain free from it.

The findings obtained in the patients examined can be summarized as follows (see Figs. 4, 6 and 1).

- 1 Dominant autosomal transmission
- 2 The first manifestation probably comes in the second decade the youngest patient being 13 years of age (VII 39)
- 3 The corneal opacities are mostly subepithelial some are localized in the corneal stroma about halfway in its depth
The subepithelial opacities present the appearance of candlegrease spots sugar crystals or thin lines the more deepseated opacities are for the most part spider-like The number varies widely Linear structures decrease as the severity of the corneal dystrophy increases
- 4 The dystrophy generally avoids the axial region and does not affect the limbus either From the bottom it spreads fan wise to the upper nasal and temporal areas and therefore it is somewhat reminiscent of cornea verticillata
- 5 There is no corneal vascularization or photophobia Corneal sensitivity is not reduced no attacks of pain occur and there are no epithelial defects The histories show that patients are unaware of the fact that they suffer from an eye disease
- 6 The visual acuity is generally normal even at a more advanced age Only in case VI 28 could diminished visual acuity (0.8) be ascribed in any sense to the corneal dystrophy
- 7 The histology is quite unknown because so far there has been no indication for an optical keratoplasty The biopsy of the sural nerve in VI 28 did not disclose storage in the form of mucopolysaccharidosis

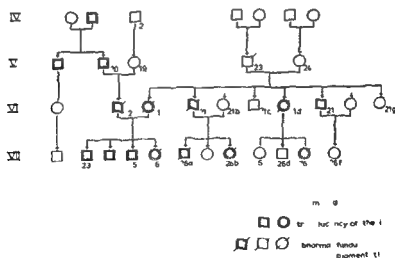


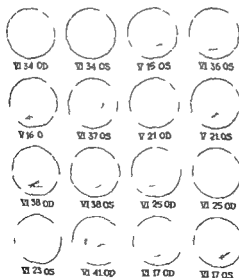
Fig 2
Pedigree showing the inheritance of albinism see also Fig 1



Fig 6

Artist's drawing of corneal dystrophy patient No VI 98

Precise classification of the corneal dystrophy here described is difficult because invariably there are differences from the known dominant autosomal dystrophies. As we mentioned the configuration of the dystrophic areas is somewhat reminiscent of Fleischer's vortex dystrophy but the appearance of



Fig

Schematic representation by the author of the corneal dystrophy in some patients

the opacities is quite different. As the epithelium remains entirely intact the possibilities described by Biber Harab Dimmer Meesmann Reis Bucklers and Waardenburg-Jonkers are ruled out. The appearance and the localization of the opacities are not readily consistent with François fleck dystrophy or Schnijder's dystrophy. The only remaining possibility is a granular dystrophy (Groenouw type I), but this dystrophy differs from that described by us in that granular dystrophy develops to form a disc in the axial region during the third or fourth decade. In older individuals the epithelium is somewhat irregular and painful episodes and recurrent erosions may occur. In actual fact our only argument to identify this dystrophy as a Groenouw type I is based on the illustration in Vogt's publication (1930 Figs 226a and 226b). Vogt describes this picture as the earliest stage of granular dystrophy characterized in particular by linear opacities. Applying this criterion to our particular family we conclude that the corneal dystrophy we observed might be a type of granular dystrophy which has not yet fully developed.

Tapetoretinal degeneration

This occurs in only one sibship. Consanguinity between V 19 and V 20 has not been demonstrated but since identical surnames traceable to the same place of residence have been found among the respective ancestors we hope to be able to demonstrate that consanguinity may be present after all.

The central component of tapetoretinal degeneration leads to an acquired achromatopsia; the features resemble those of a juvenile macular degeneration as described by Stargardt. The peripheral component is atypical in so far as the pigment configuration is concerned for the typical trabecular pigmentations are only observed in one patient and at that in small numbers. However in our opinion there is no reason to divide the condition into juvenile macular degeneration combined with atypical peripheral retinal pigmentary atrophy in all patients alike; it becomes manifest as a diffuse tapetoretinal degeneration.

Albinism

The principal symptoms relating to albinism are schematically presented in Fig 5. The father of case V 20 is unfortunately deceased but was known among his friends when alive as 'Whitey'.

Fig 5 indicates recessive autosomal albinism with cases VII 23 and VII 24 as homozygotes; the remaining patients should be regarded as heterozygotes. The findings obtained in the heterozygotes vary; the characteristics being a) translucency of the iris b) abnormal fundus pigmentation c) ginger hair (only in case VII 26) or fair hair.

Translucency of the iris is the most common sign which seems to be more constant than abnormal fundus pigmentation. The latter moreover is less pronounced than that observed in carriers of recessive x chromosomal ocular albinism. The fair hair also is found in individuals showing no other signs of heterozygotism and this feature is therefore unreliable.

To try to gain an impression of the value of translucency of the iris we examined a random group of 80 females aged 18-35.

Bilateral translucency of the iris was observed in 4 individuals. 2 patients proved to be carriers of ocular albinism, one had ginger hair as well and one showed evidence of a bilateral posterior cyclitis in the past.

Waardenburg (1970) found translucency of the iris also in heterozygotes of recessive autosomal albinism. Froggath (1960) maintained that the iris translucency need not always be present. François (1972) describes an abortive form of recessive autosomal albinism in which translucency of the iris occurs in the parents but is not found as a general rule.

In view of these data from the literature our findings may not be generalized to mean that translucency of the iris is as a rule a characteristic of heterozygotes in recessive autosomal albinism. nevertheless the findings we obtained with our family do warrant a conclusion that there is intermediate transmission.

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PTERIONAL ORBITAL DECOMPRESSION IN PROGRESSIVE OPHTHALMOPATHY OF GRAVES DISEASE

I Short Term Effects

BY

P ALGVERE S ALMQVIST and E O BACKLUND

Twenty seven patients with Graves disease and progressive ophthalmopathy in an advanced stage underwent a transtemporal orbital decompression. The short term results i.e. within 9 months of 43 operations are reported.

Prior to the decompression oral prednisolone 90-60 mg daily was given for 9 to 9 months to 15 patients. A minority of patients experienced temporary improvement during steroid administration. Cushing's syndrome was initiated in all patients. Prednisolone little altered the course of the progressive ophthalmopathy.

Orbital decompression was followed by increasing visual acuity in 8/22 eyes with disturbed vision, a temporary decrease in 11 eyes and unaltered visual acuity in the remaining 8 eyes. The decompression removed oedema of the optic disc in all eyes, cured glaucoma in 3 out of 5 patients, caused retraction of the eye bulbs by 5-6 mm in almost all operated cases and increased compressibility of the orbital content from low (2-5 mm) to normal (6-10 mm) values. Surgery also relieved photophobia and lacrimation but the effect on diplopia was uncertain. Generally the decompression was followed by a rapid improvement of the orbital congestion and the patients recovered satisfactorily from the surgery.

Key words: endocrine ophthalmopathy - exophthalmos - Graves disease - pterional orbital decompression - corticosteroid treatment - intraorbital pressure - orbitonometry

Many methods have been advocated for the treatment of infiltrative endocrine ophthalmopathy with severe proptosis (leading article *Brit Med J* 3 565 1968). It is necessary to relieve pain and discomfort and prevent the sequelae of lagophthalmos, elevated intraocular pressure and optic nerve involvement. Topical treatment is directed mainly against the local changes in the eye and is insufficient to cure the basic disease.

In an attempt to improve the orbital condition, treatment with large doses of corticosteroids, e.g. 40–60 mg prednisolone daily, has been advised (Werner 1966; Day & Carrol 1968; Bonnyns et al 1968; Marcouli & Dellaporta 1969) but such therapy will soon result in symptoms of Cushing's syndrome which makes long term treatment difficult or impossible. Corticosteroid treatment of other conditions (not Graves' disease) was followed by exophthalmos (Slansky et al 1967).

The effect of irradiation on the pituitary gland or the retrobulbar orbital space remains dubious.

In advanced cases where the risk of visual loss is imminent, surgical intervention by decompression of the bony orbit has been advocated in order to create space for the enlarged orbital contents. A lateral orbital approach was introduced by Krönlein (1889) and has since been performed with several modifications, all of which consist principally of a lateral wall resection (Berke 1954; Knauer 1957; Kroll & Casten 1966; Long & Ellis 1966). Naffziger & Jones (1932) used a transfrontal craniotomy, an intradural procedure resulting mainly in removal of the orbital roof. Welti & Offret (1943) described a pterional transtemporal approach permitting a combined resection of the lateral and superior walls of the orbit and performed as an entirely extradural operation (Hamby 1964). By means of a lateral orbital approach, also parts of the lateral and superior walls can be removed (Dickson Wright 1945; Moran 1956; Stallard 1958). Even transantral orbital decompression is used (Stell 1965).

We have recently reported a high incidence of hypothyroidism in patients with endocrine ophthalmopathy (Almquist & Algvere 1972). The increased tissue volume which occurs in hypothyroidism may produce an increase in intraorbital pressure. Therefore, pterional orbital decompression was performed when other therapeutic measures including administration of 200 µg or more of thyroxine and corticosteroids had failed. The aim of this paper was to present the transient effects of steroid administration and the short term results of orbital decompression.

Case Material

In 97 patients (21 females and 6 males) with progressive endocrine ophthalmopathy after Graves disease a periorbital decompression of the bony orbit was performed. Surgery was carried out in 48 orbits bilaterally in 21 patients and was limited to one orbit in 76 patients. The patients' ages at the time of orbital decompression varied from 31 to 71 years (average 53).

The duration of ophthalmopathy mainly exophthalmos averaged 2.7 years (range 1/9 - 10 years). Various ocular lesions which interfered with the normal function of the eye had been known to exist for an average of 2 years. These lesions included diplopia or restricted motion of the eyes, lagophthalmos and keratopathy, reduction of visual acuity or fields and fundus changes.

Methods

Ophthalmologic examination. Pre- and postoperative examinations included visual acuity, visual fields, biomicroscopy and ophthalmoscopy, Schiøtz tonometry, Hertel exophthalmometry, observations on diplopia and ocular motion. In selected cases the examination was extended to an investigation for glaucoma (applanation tonometry, tonography, provocation tests, etc.), orbitonometry according to Copper (1948), evaluation of diplopia by the measurement of angles of deviation (prisms), mapping on Lees screen, forced duction test, x-ray of the orbit and sella turcica.

Therapeutic methods. For treatment of the endocrinologic disease the following procedures were used according to the needs of each patient: subtotal resection of the thyroid gland, administration of therapeutic fractionated doses of ^{131}I , substitution therapy with synthetic thyroid hormones, treatment with antithyroid drugs such as thiouracil 100 mg 4 times daily.

For the ophthalmopathy cure was sought from the following methods: Topical medical treatment of the eyes by currently used eye drops and ointments to relieve symptoms and suffering. Miotics, Eppy® (Pharmacia) or carbonic anhydrase inhibitors were used to control elevated intraocular pressure.

Oral treatment with prednisolone 40-60 mg daily was given to 15 patients when the orbital disease progressed.

X-irradiation and ^{60}Co treatment 4 000 rad tumour dose against the pituitary gland and the retrobulbar orbital space (Dahl 1960) was given to 3 patients.

Lateral decompression of the orbit according to Weltz & Offret (1943) as performed by Backlund (1968).

Surgical procedure General anaesthesia with controlled respiration and moderate hyperventilation was used routinely. If the patients' eye lids closed spontaneously they were secured in this position with surgical tape but if they had a tendency to separate a tarsorrhaphy was performed. The pterional region was reached by making a curved incision over the temporal fossa and by splitting of the temporal muscle in the direction of its fibres. The orbitotomy was performed by removing the large sphenoid wing. This was easily reached from the pterion bone if the extradural space was exposed via one burr hole on each side of the fissure of Sylvius.

The lateral wall of the orbit was resected posteriorly to the lateral extensions of both orbital fissures and part of the orbital roof was removed. The extent of the bone removed will determine the volume of the orbit and the effect of the decompression. The bone defect obtained is seen in Fig. 1.

When the orbitotomy was completed the orbital fascia was opened and torn in all directions allowing the orbital fat to prolapse extensively. This tearing should be performed with the fascia carefully separated from the orbital contents by blunt dissection. Special care was devoted to the supraorbital nerve and the superior palpebral levator muscle.

After careful haemostasis the wound was closed in layers over a rubber drain. Surgery could be performed on both orbits during the same period of narcosis. However, most patients were operated on twice with an interval of at least 1 week between the decompressions. The incision was closed and a

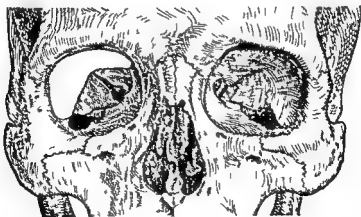


Fig. 1

Drawing of the bone configuration of the orbits. The white area at the upper temporal part of the right orbit shows the size of the bone removed by pterional orbital decompression. The lateral wall of the orbit is resected as far anteriorly as to the zygomatic arc and downwards to the inferior orbital fissure.

pressure bandage applied over the eyelids. The bandage was changed every other day and was removed after 5-6 days as was the tarsorrhaphy or the tapes closing the lids. For the final results the fitting of this pressure bandage was of great importance. Also individual plaster casts have proved useful as face masks.

Indications for pterional decompression

When all other therapeutic procedures failed a pterional decompression of the orbit was considered necessary.

The principal indications for decompression of the orbit were decreasing visual acuity or visual fields, oedema of the optic disc, exposure keratopathy and progressive proptosis with severe discomfort.

The following distribution of these symptoms and signs was found in the 48 eyes operated on:

Decreasing visual acuity	22 eyes
Oedema of the optic disc	9 eyes
Keratopathy in lagophthalmos	12 eyes
Progressive proptosis with severe discomfort	34 eyes

In most patients two or more changes were present justifying the operation. At the time of orbital surgery all patients had been on sick leave for a considerable length of time.

Observations and Results

Effect of corticosteroid treatment

Prednisolone was given to 15 of our 30 patients in doses of 30 to 60 mg daily for 2 to 9 months (Table 1). Four of these 15 patients showed temporary decrease of proptosis, two patients gained temporary increase of visual acuity and 3 patients experienced relief from their discomfort. Thus no permanent amelioration of any sign was caused by prednisolone in these severe cases and there was no change from a malignant to a benign course of the disorder. All patients developed an iatrogenic Cushing's syndrome which made long term treatment impossible.

Effect of orbital decompression

Visual acuity. Reduction in visual acuity of $\frac{3}{10}$ or more from the original value was considered to be an indication for orbital decompression. Preoperative visual acuity (corrected with glasses) had a range of 0.1-0.7 and the

Table I

Effects of administration of prednisolone to euthyroid patients with progressive ophthalmopathy

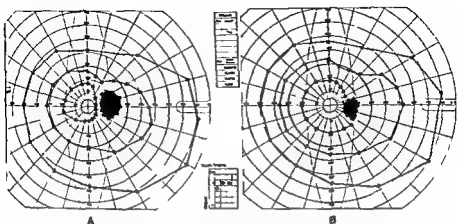
Patient's initials	Eye No	Prednisolone		Improvement of			Cushing's syndrome
		Dose mg	Time months	Proptosis mm	Reduced visual acuity	Other symptoms	
B A	7 + 8	15 × 3	> 2	0	0	0	+
S A	9	20 × 3	> 2	0		discomfort	+
A B	12 + 13	10 × 4	> 2	26/23 → 22/23		discomfort	+
S C	14	10 × 4	> 2	22 → 18		0	+
I E	15 + 16	10 × 3	6	0		0	+
K H	19	10 × 3	> 2	0		0	+
S H	20 + 21	10 × 4	6	0	0	0	+
E N	29	10 × 4	> 2	22 → 19	+ (1)	discomfort	+
K S	32 + 33	20 × 3	4	0	+ (2)	0	+
A S	34 + 35	5 × 4	> 2	0	0	0	?
I U	40 + 41	10 × 4	5	26/26 → 22/24		diplopia	+
E L	42 + 43	10 × 3	> 2	0	0	discomfort	+
L P H	50	10 × 3	5	0		0	+
G S	51	10 × 4	9	?	0	0	+
S O	52	10 × 3	> 6	0		0	+
Sum n = 15				1/15	2/3	5/15	14/15

(1) Visual acuity increased temporarily from R=0.5 L=0.4 to R=1.0 L=0.1

(2) Visual acuity increased temporarily from R=0.2 L=0.4 to R=0.9 I=0.6

mean value was 0.5 (n = 22). Since the postoperative irritation was disturbing for the first weeks after surgery reliable values for visual acuity were not obtained for all patients during that period. The values that were recorded showed however that 6 to 28 days after surgery the visual acuity had increased in 8 eyes, had temporarily decreased in 6 eyes and was essentially unaltered in the rest of the cases. However an unequivocal increase in visual acuity was noted on follow up examination 1½ - 4 years later.

Visual fields - In four patients paracentral or arcuate scotomas were found on perimetry although intraocular pressure was normal. In cases with a choked disc enlargement of the blind spot occurred and after decompression regression of visual field defects was noted (Fig. 2). In cases of co existing glaucoma various defects of visual fields characteristic of this disease were mapped.



Fig

Visual field defects in malignant endocrine ophthalmopathy

A Goldmann perimetry of right eye (16 June) before surgery shows enlargement of blind spot and reduction of the area within central isopters. Visual acuity was 0.6

B Perimetry of right eye (19 July) 3 weeks after orbital decompression. There was a recovery of central retinal sensitivity. Visual acuity 0.8

Optic disc On preoperative examination oedema of the optic disc was encountered in 1 patient (9 eyes) and in one of these eyes peripapillary bleedings were seen. Engorgement of retinal venules was evident in another 2 patients (4 eyes). Atrophy of the optic nerve without co-existing elevation of intraocular pressure was found in 1 patient (2 eyes). However pallor of the optic disc was present in 4 other patients with glaucoma. Oedema of the optic disc subsided in all cases after orbital decompression (Fig 3).

One patient (R J) had bilateral oedema of the optic disc before surgery. After decompression of his left orbit the optic disc became normal. However oedema of the optic disc persisted in his right eye.

Glaucoma - In 5 patients there was an elevation of intraocular pressure to such a level that a diagnosis of glaucoma was considered justified (28 mm applanation or more). In these eyes the chamber angle was wide and the facility of outflow within normal values. The effect of miotics in reducing ocular tension was insignificant and carbonic anhydrase inhibitors were administered.

After orbital decompression there was a remarkable lowering of ocular tension in 3 patients and the anti glaucomatous therapy was soon abandoned. In 2 cases however the increased ocular tension persisted and required further treatment.

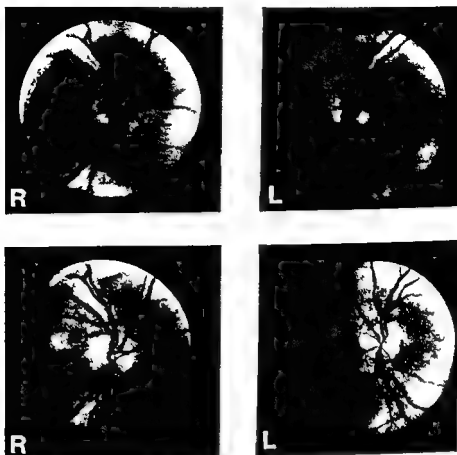


Fig 3

Remission of choked disc in malignant endocrine ophthalmopathy after bilateral orbital decompression. Fundus photographs of right and left eye before surgery (upper figures) and 2 months after surgery (figures below). The visual fields of right eye are shown in Fig 2.

Proptosis. All patients except 2 displayed considerable proptosis apparent on mere inspection and on exophthalmometry as well (The 2 patients mentioned underwent orbital decompression for decreasing visual acuity). In most cases of marked proptosis there was heavy oedema of the eye lids, chemosis, lagophthalmos and other signs accompanied by severe discomfort of lacrimation and photophobia (Class 3b = see Werner 1969). Generally, progressive proptosis *per se* was considered for surgery provided that Hertel readings of 25 mm or more were present. Actually, only 2 patients underwent orbital decompression for cosmetic reasons, that is, progressive proptosis without functional disorders (Class 3 2a 5c).

Preoperatively, repetitive Hertel readings of 25 mm or more were found for

30 eyes and 20-24 mm for 15 eyes. After orbital decompression there was a striking regression of proptosis and Hertel readings evident on the 5th or 6th postoperative day. In the group of eyes where preoperative Hertel readings were 25 mm or more postoperative retraction of the bulbs averaged 5.7 mm. In the rest of the eyes the mean retraction was 4.0 mm.

Orbitonometry The compressibility of the orbital contents was studied by orbitonometry according to Copper (1948). The dynamometer used produced pressures up to 400 ponds on a contact shell resting on the eye.

Moderate or advanced proptosis was present in the 9 patients studied (17 eyes). In 11 eyes the orbitonometric values were pathological according to Copper. The remaining cases also showed a flattened curve of the plotted measurements, the orbitonometric readings usually being near the lower limit of normal values.

On postoperative examination there was a significant and large increase in the compressibility of orbital contents in patients with initially low and pathological orbitonometric values, and normal orbital resiliency was demonstrated (Fig 4). This was also shown by the absolute values obtained by orbitonometry (see Fig 5).

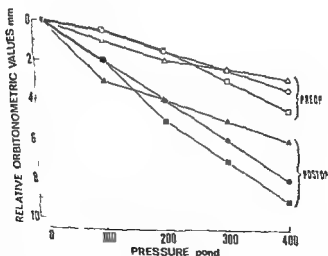


Fig 4

Increase in compressibility of the orbital tissues in three patients plotted as relative orbitonometric values according to Copper before and after orbital decompression. Each line represents one patient and shows low values before (open symbols) and normal readings (black symbols) after surgery.

A 60 year old woman (G B) presented considerable proptosis (Class 3 3 c ° b) and elevated orbitonometric values. Seven days after orbital decompression the proptosis had regressed, the absolute orbitonometric values had diminished and the orbital resiliency was normalized (Fig. 5).

When the preoperative orbital resiliency was normal or at the lower limit of normal values the increase in compressibility was only slight or moderate. If a marked fibrosis of the orbital contents was present no increase in orbital resiliency resulted from the operation (as illustrated by the following case).

A 58 year old woman (S O) had a history of 2 periods of hyperthyreosis during 4 years. Preoperative Hertel readings were 30–31 mm and orbitonometry showed a compressibility of orbital contents of 5½ mm (at a pressure of 400 ponds). During surgery it was observed that the orbital tissues did not prolapse through the incision made into the orbital fascia, the orbita showing fairly nonelastic and indurated contents. On postoperative examination the Hertel values had diminished to 23 mm but the orbitonometric readings showed a compressibility of 8 mm (at a pressure of 400 ponds) the same value as obtained preoperatively.

As a rule a diminution of the orbital resiliency occurred after the lateral decompression. The largest compressibility obtained was 9 mm, a reading which is within the normal range. This implies that the pterional decompression does not lower orbital tension to a pathological degree nor does it disturb the balance of pressure between the orbital and cerebral cavities.

Exposure keratopathy. When a keratopathy had developed a co-existent proptosis and lagophthalmos of considerable severity was the rule. The kera-

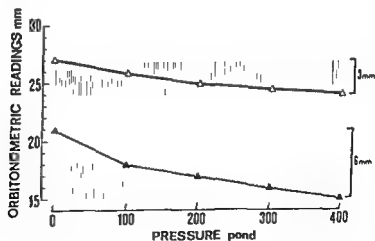


Fig. 5

Orbital resiliency in a patient (G B) measured by orbitonometry according to Copper. Before surgery proptosis and high orbital resiliency was recorded (Δ). Seven days after orbital decompression proptosis decreased and normal orbitonometric readings were obtained (▲). Initial orbitonometric readings are comparable to Hertel values.

topathy was usually localized in the inferior exposed quadrant of cornea insufficiently covered by the eye lids. Corneal changes staining with fluorescein were observed in 13 eyes. A temporary improvement was achieved by topical treatment and tarsorrhaphy but the disease was recurrent. After lateral decompression of the orbit the corneal disease usually healed. In two eyes however the keratopathy soon recurred in one eye as a herpetic ulcer.

The operative procedure *per se* was accompanied by certain corneal changes. During the first postoperative week corneal erosions and in some cases stromal cloudiness as well as pathology of Descemet's membrane were observed. These changes were considered to be due to the compression caused by the bandage. They healed in 7-10 days after the bandage was removed leaving peripheral superficial scars in a few eyes.

Ocular motion and diplopia Involvement of the extrinsic eye muscles was common. Before the orbital operation 22 of 27 patients had diplopia in some direction and 17 of them suffered from diplopia even when looking straight forward.

Some restriction of ocular motion was found in the overwhelming majority of cases. The most common finding was a limitation of elevation which was encountered in 19 cases. Insufficient abduction was present in 13 patients 11 of whom also displayed limitation of adduction. In the latter cases the motion of the bulbs was limited also in the vertical direction and the eyes appeared almost motionless.

After orbital decompression an alteration in the diplopia was reported by most patients during the postoperative period. Four patients considered their discomfort from diplopia to be definitely worse than before the operation.

Lid oedema and chemosis of conjunctiva - After orbital decompression oedema of the eye lids regressed rapidly as did chemosis of the conjunctiva. In most cases the signs of orbital congestion disappeared during the first postoperative month.

Subjective discomfort - In cases of moderate or pronounced proptosis the oedema of the eye lids and the chemosis of the conjunctiva were often accompanied by severe discomfort including pain photophobia and lacrimation.

Many patients related a feeling of oppression or tightness in the orbit or headache in the temporal region. A minority of patients described true pain often throbbing in character localized in the eye bulb or orbital region.

Photophobia was a common complaint despite the absence of keratopathy or anterior uveitis. Very many patients felt severe ocular discomfort as in dazzling sunshine and suffered sufficient irritation to warrant wearing tinted glasses also indoors. Much lacrimation was often elicited by light or wind. In

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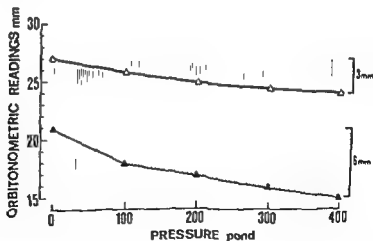


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be expected. In long standing orbital disease with chronic congestion few if any beneficial effects of such therapy remained when corticosteroids had been discontinued.

Orbital decompression by the pterional route resulted in significant improvement of all the deleterious sequelae of the ophthalmopathy as long as these complications were within a reversible range. The previously reduced visual acuity improved, oedema of the optic disc subsided and the accompanying visual field defects (enlarged blind spot) regressed.

Lowering of intraocular pressure occurred in the few cases of glaucoma studied. The incidence of open angle glaucoma is considered to be 1-2% in persons over 40 years of age (Duke Elder 1969). In our case material a considerably higher prevalence of glaucoma was encountered (5/34 cases). Pohjanpelto (1968) found the incidence of glaucoma to be 8.3% in hyperthyroid patients over 40 years of age.

There was generally a significant regression of the advanced proptosis averaging 5-6 mm according to Hertel readings. It is interesting to note that Moran (1954) obtained the same result by a similar operation. The concomitant oedema of the eyelids and chemosis of conjunctiva also subsided. The healing of corneal changes seemed to be accelerated. There was also a remarkable relief from orbital discomfort and pain and of lacrimation and photophobia as well. In some cases retraction of the eye bulbs was not at all impressive as judged from Hertel readings. Yet the subjective improvement and reduction of discomfort were encouraging and the final symptoms if any were often dismissed as negligible by the patients.

The orbital decompression was of little value regarding indurated changes of the eye lids and lid retraction. Diplopia usually was altered by orbital surgery but this change was favourable only in a minority of patients. Some patients regarded their diplopia as considerably worse after this operation and had to learn to suppress their new type of diplopia.

Generally the best results were obtained in patients operated on early in the course of their progressive ophthalmopathy i.e. prior to the development of fibrotic orbital changes.

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17 of 23 patients spontaneous lacrimation of pathological degree was present with a flow of tears on the face without any extrinsic reason. Most of these cases exhibited lagophthalmos. The epiphora was exaggerated when the patient was lying down and some patients preferred to sleep in a sitting position.

Surgical complications and sequelae

A postoperative liquorrhoe appeared in 2 patients but was cured by lumbar puncture. One case of pulmonary embolism occurred from which the patient recovered. In another patient peripheral palsy of the facial nerve was observed (limited to the forehead) and was probably due to the surgical wound. As previously mentioned certain corneal changes were caused by the compression bandage. In a 61 year old woman with glaucoma and visual field defects an intraorbital haemorrhage developed postoperatively and was followed by proptosis and optic nerve atrophy. As observed by Kroll & Casten (1966) a choked disc associated with incipient optic nerve atrophy may progress to blindness despite decompression of the orbit.

Small but distinct ocular pulsations were visible on inspection of three eyes. No harmful effects of this were noted.

Generally the patients recovered rapidly from the orbital decompression.

Discussion

Topical medical treatment to palliate ocular changes resulted in temporary relief of some of the symptoms and suffering in many patients. The management of acute keratopathy was facilitated by tarsorrhaphy. Elevated intraocular pressure could be controlled especially by carbon anhydrase inhibitors. However in the majority of patients topical treatment of the eye was insufficient to alter the duration and course of the ophthalmopathy.

Treatment with large doses of corticosteroids was followed by a relief of discomfort, decrease of proptosis and improvement of visual acuity in a minority of patients. But signs and symptoms of Cushing's syndrome developed regularly and prevented further treatment.

After cessation of corticosteroid administration a deterioration of the orbital condition occurred. If this treatment could have been continued more favourable results might have been obtained. It is plausible that in milder cases of infiltrative ophthalmopathy acute exacerbations of the orbital disease can be controlled by corticosteroids. After that the disease may even spontaneously take on a milder character. The more the fibrotic changes in orbital tissues have developed the less the effect of corticosteroid treatment that can

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PTERIONAL ORBITAL DECOMPRESSION IN PROGRESSIVE OPHTHALMOPATHY OF GRAVES DISEASE

II A Follow Up Study

BY

P ALGVERE S ALMQVIST and E O BACKLUND

Twenty seven patients with Graves disease and progressive ophthalmopathy in an advanced stage underwent a transtemporal orbital decompression. The long term effects i.e. after 1½-7 years are reported. As a rule the beneficial results of the surgery were stable and long lasting. Visual acuity improved in 20 of 22 eyes in which it was reduced preoperatively. Regression of proptosis persisted in the majority of patients. The surgery permanently relieved photophobia in 17 patients and larmimation in 18 of 27 patients.

Key words: endocrine ophthalmopathy - exophthalmos - Graves disease - pterional orbital decompression - long term effects

In advanced stages of endocrine ophthalmopathy in which the orbital disease causes deteriorating ocular functions a decompression of the bony orbit is able to improve the clinical condition. Removal of part of the lateral and superior orbital wall creates a larger space for the orbital contents. Favourable short term results of such surgery were a rapid regression of the signs of orbital congestion as reported by Algvere, Almqvist & Backlund (1973).

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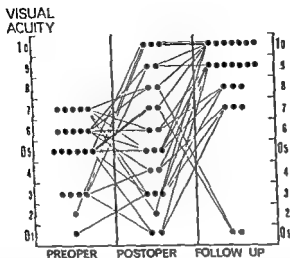


Fig 1

Long term observations on visual acuity in 99 eyes that preoperatively had a reduction of visual acuity of 3/10 or more. Postoperative period of observation was 6-93 days. Follow up examination was performed 1 1/2- years after orbital decompression. Each dot on the figure represents one eye.

a keratopathy with corneal cicatrization on their operated eyes. During the postoperative period their vision had recovered satisfactorily (to 0.7 and 0.8 respectively).

Also in the rest of the patients with a preoperative visual acuity of 0.7 or more the final vision was normal with the exception of one patient. Preoperatively this patient had had a pallor of the optic disc and her visual acuity was 0.8. She developed an optic atrophy and 3 years later at the follow up examination the visual acuity was 0.2.

Proptosis. One of the features in this case material was the severe exophthalmos. All but two patients exhibited a marked proptosis with all its disturbing and irritating sequelae.

The favourable regression of proptosis which followed the orbital decompression was generally stable and longlasting. At the follow up examination the majority of eyes were in the same position as they had been during the postoperative period. The long term results in those eyes where preoperative Hertel readings were 25 mm or more are shown in Fig 2. In a few instances however a slight progression of proptosis had occurred.

The underlying endocrinologic disease might have a very long duration. A hypothyroidism often develops after treatment for Graves' disease and was found to accompany the exacerbations of infiltrative or malignant ophthalmopathy (Almquist & Algvere 1972). All hypothyroid patients were substituted with thyroxine and became euthyroid. The long term effects of the orbital decompression were followed in order to assess whether or not the orbital surgery could prevent further recurrences of progressive ophthalmopathy. In the present paper the results of a follow up examination performed 1½-7 years after the orbital decompression are reported.

Material and Methods

Twenty seven patients (21 females and 6 males) who developed infiltrative or malignant ophthalmopathy after Graves' disease underwent orbital decompression via the periorbital route during the period of 1964-1970 as previously described (Algvere, Almquist & Backlund 1973). There were 48 such operations. The patients' ages at the time of orbital surgery varied from 31 to 71 years (average 53 years).

All patients had been under continuous medical and ophthalmological control. The follow up examination was carried out in 1971 i.e. 1½ to 7 years after orbital surgery. The patients were questioned about their remaining discomfort and whether in their opinion the ocular condition was improved or not. The ophthalmological examination included determination of visual acuity and fields, biomicroscopy with the slit lamp, ophthalmoscopy, Schiotz tonometry, Hertel exophthalmometry and observations of diplopia and ocular motion. If the findings so indicated, additional examinations were performed.

Observations and Results

Visual acuity. In 22 eyes there was a preoperative reduction of visual acuity of 3/10 or more. At the follow up examination it was found that visual acuity in almost all eyes in this series had increased and normalized at 0.1-1.0. The most impressive improvement of course was seen in those cases with the deepest preoperative reduction (Fig. 1).

The final results remained unsatisfactory in two eyes. Both patients showed

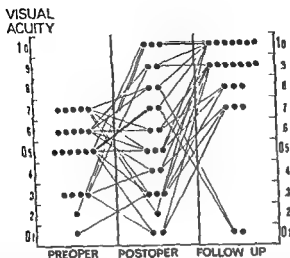


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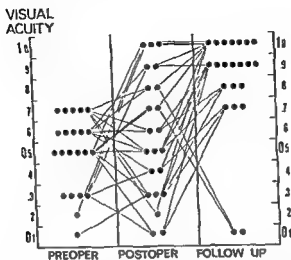


Fig 1

Long term observations on visual acuity in 2 eyes that preoperatively had a reduction of visual acuity of 3/10 or more. Postoperative period of observation was 6-93 days. Follow up examination was performed 1½-7 years after orbital decompression. Each dot on the figure represents one eye.

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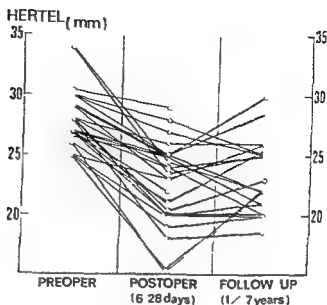


Fig 2

Long term observations on proptosis of 27 eyes that preoperatively had Hertel readings of 25 mm or more. Each line on the figure represents one eye.

Also in the group of eyes with preoperative Hertel readings of 20-24 mm the postoperative results generally lasted for a long time and were essentially the same (increase 2 mm or less) at the follow up examination. In only one eye of this group did Hertel readings increase as much as 4 mm during 5 years; the reason for this was not plain but a hypothyroidism was later found in this patient.

In many patients the regression of proptosis by a few mm was not at all impressive. Nevertheless these patients showed as well as did others with a greater retraction of the bulbs a remarkable improvement of several of the sequelae of the orbital disease. As a rule the oedema of the eye lids, the congestion of the episcleral veins and the conjunctival hyperemia had disappeared. Only a few patients still showed venous congestion at the nasal part of the conjunctiva at the follow up examination.

Despite the fact that many eyes after the decompression still showed Hertel readings at a pathological level the clinical improvement noted during the postoperative period turned out to be stable and longlasting.

Keratopathy. Before the orbital decompression 13 eyes showed corneal changes staining with fluorescein and these eyes healed during the postoperative term. In 11 of these 13 eyes no keratopathy later occurred.

On follow up examination no active keratopathy was encountered in the whole case material except in two eyes. One case had a long lasting herpetic corneal disease. The other patient also suffering from diabetes mellitus developed a large vascularized corneal ulcer, an anterior uveitis and a cataract. During the postoperative term his cornea showed satisfactory improvement.

Diplopia. Twenty two of 27 patients had diplopia in some direction of their gaze before the orbital decompression and at the follow up examination 13 patients declared that they still had this symptom (Table I). Some limitation of ocular motion remained in 16 patients. In 7 instances the diplopia was improved in the sense that the patients were not aware of it at least not when looking straight forward although it could be provoked in most of them by deviation of their gaze. Therefore several patients considered their diplopia only as a slight discomfort.

The effect of orbital decompression on diplopia varied. When symptoms and signs of severe myopathy of the extrinsic eye muscles were present no significant improvement of diplopia was attained. The results were more favourable in a minority of patients who originally had heterophoria or strabismus with small angles of deviation. At the follow up examination most of these patients declared that they had no diplopia when looking straight forward.

The surgical correction of the combined involvement of horizontally and vertically acting eye muscles was difficult and often disappointing. The effect of the myopathy was irregular and asymmetric. Only in cases of isolated and pure vertical diplopia due to insufficient elevation of the eye did surgery prove successful. In these cases a significant loss of passive stretch in the inferior rectus muscle was always present. This was evaluated with the forced duction

Table I
Effects of orbital decompression on some ocular symptoms and signs

	Before orbital decompression	At follow up examination
Restricted eye motility	19 patients of 27	16 patients of 27
Permanent diplopia	25 patients of 27	13 patients of 27
Pain	6 patients of 27	4 patients of 27
Photophobia	13 patients of 27	7 patients of 27
Lacrimation	17 patients of 27	8 patients of 27

test when moving the eye with a forceps or during surgery by means of a muscle hook placed under the inferior rectus. This muscle was fibrotic non elastic and very difficult to stretch and seemed to prevent elevation of the bulb. The diplopia was often cured by recession of the inferior rectus muscle. After that the elevating eye muscles showed almost normal action (cf Long & Ellis 1966). The insufficient elevation was probably caused by myopathy of the inferior rectus and not primarily by paralysis of the elevation muscles.

Subjective discomfort. On follow up examination the patients were questioned about their remaining discomfort and whether in their opinion their complaints were alleviated soon after the orbital decompression. Four patients considered the surgery of no beneficial value, two patients were uncertain and the rest of them (21 patients) believed that they had gained relief from their severe discomfort. Some patients still had pain or "head ache" in the orbital region. There was however remarkable regression of lacrimation and photophobia (Table I). This was consistent with the findings that the signs of orbital congestion had disappeared.

Discussion

The follow up examination showed that the beneficial effects obtained after orbital decompression such as increase of visual acuity, regression of proptosis and improvement of other sequelae of orbital congestion generally persist for a considerable time. This was also observed by Morin (1956) in a 9 year period of follow up examinations. Long & Ellis (1966) concluded that 98 of 40 operated patients derived some benefit from surgery and observed visual improvement in 14 of 18 eyes. Kroll & Casten (1966) reported favourable results in a series of 18 patients (32 lateral decompressions); there was an improvement of visual acuity in 19 of 26 eyes after surgery.

The pathological changes that occur in endocrine ophthalmopathy display oedema and infiltration by inflammatory cells in retrobulbar tissues (Falconer & Alexander 1951, McCrugg & Dodge 1952, Tengroth 1961, 1964). In long standing cases a fibrosis develops (Ridley 1952). Essentially the same pathology was encountered in experimental exophthalmos induced in guinea pigs (Smelser 1962). Myopathy of the extrinsic eye muscles develops and a tremendous increase in their volume up to 2-5 times their normal bulk has been observed (Naffziger 1933). Under such circumstances circulatory congestion may easily occur in the orbit. In addition the orbit lacks lymph drainage (Duke Elder

1961) Orbital tissues show increased content of water (Smelser & Ozanics 1959) and this has been ascribed to permeability changes in orbital capillaries (Prame 1969) A venous stasis in orbital tissues has been demonstrated by clinical self limiting condition After periods of months or years some remission may then develop rapidly and cause sudden deterioration of the ocular disease as observed in this case material and described by others (Ehlers 1968 Haddad 1968)

It has often been stated that infiltrative endocrine ophthalmopathy is a self limiting condition After periods of months or years some remission may occur followed by a stationary stage characterized by exophthalmos and disturbances of motility (Rise 1970) The course of ocular proptosis in patients with Graves disease shows however that proptosis tends to increase or remains unchanged in the majority of cases For example Hales & Rundle (1960) observed that in 99 of 105 patients proptosis increased (24 cases) or remained unchanged (15 cases) Hamilton et al (1960) also stated that proptosis in 91 % (160 patients) remained static or increased Jones et al (1969) found that 3 % of 36 patients showed a regression of proptosis during a period of 3-6 years This is consistent with the observations in our case material There was no spontaneous improvement of proptosis or cure of malignant signs during a period of observation averaging 2 1 years

Evidently medical treatment alone is insufficient to cure progressive ophthalmopathy in the late stage of the disease The acute orbital oedema will after periods of months or years cease to progress and finally even regress However fibrotic changes in retrobulbar tissues will develop and remain stationary causing considerable suffering and deterioration in ocular function Consequently orbital decompression seems necessary to restore the eye to its original position This is advisable since these patients run the risk of recurrent hyperthyroidism or periods of untreated hypothyroidism resulting from treatment of Graves disease This might in a way still unknown cause their ophthalmopathy to deteriorate

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LISSAMINE GREEN

Vital Staining of Cornea and Conjunctiva

BY

M S NORN

The present investigation comprised 171 eyes examined in the slit lamp and 99 specimens of mucous thread epithelial scrapings and conjunctival fluid subjected to microscopy after vital staining by lissamine green, in most cases combined with rose bengal.

Lissamine green is suitable for vital staining of cornea and conjunctiva. The dye stains degenerate cells, dead cells and mucus. Its vital staining properties are almost identical with those of rose bengal.

If used successively the primarily employed component will predominate over the other.

A mixture of lissamine green and rose bengal constitutes a blue stable vital stain yielding mainly a blue colour although green and red may also be seen.

On the average 70.5% of the mucous thread is stained blue, 9.1% green and 9.5% red, the zones of different colours alternating along the length of the thread.

Key words: Lissamine green - wool green - food green - acid green - vital staining - cornea - conjunctiva - rose bengal

Lissamine green is used for colouring articles of food. It has colour index No. 44 090 and the following synonyms: wool green B, BS, BSNA or C, Pontacyl green S, Calcoid green S extra, Acid green S, Cyanol green B, fast light green, Food green.

Its formula is $C_{17}H_{12}N_2O_5S$. Molecular weight 316.6. The formula is shown in Fig. 1. It is an acid synthetically produced organic dye.

Lissamine green contains two aminophenyl groups. The dye should therefore be suspected of possibly having carcinogenic properties as in the case with tetrazolium salts for instance. However, neither carcinogenic nor toxic properties having ever been noticed, the dye is still permitted for colouring articles of food, stimulants and drugs.

Within ophthalmology, Kirk et al. have employed lissamine green for supra-vital staining of the posterior corneal surface of bank stored eyes. Kirk found weak staining only, presumably at the sites of cracks due to curving of a hypothetical membrane on the posterior surface of the corneal endothelium.

To my knowledge, lissamine green has not been employed previously for vital staining of cornea or conjunctiva.

In preliminary experiments, I noticed that instillation of lissamine green into the conjunctival sac causes no irritation and that the dye has properties very similar to those of rose bengal.

Material and Methods

A total of 171 eyes were examined. The diagnoses are seen in Table I. (Other cases include allergic conjunctivitis, pemphigoid, exophthalmos, iritis and episcleritis).

A total of 100 eyes were vital stained with 0.01 ml of a mixture of 1% lissamine green and 1% rose bengal. This mixture has a pure blue colour and is stable.

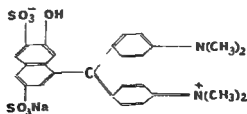


Fig. 1

The formula of lissamine green

Twenty eight eyes were given 0.01 ml of a triple mixture consisting of lissamine green rose bengal and fluorescein all in 1% concentrations. This mixture is bluish brown and becomes increasingly brown when stored.

In 13 cases 0.01 ml of 1% lissamine green was instilled first and then after 1-2 min 0.01 ml of 1% rose bengal. In 23 cases the two dyes were instilled in the reverse order.

The staining of the cornea and the conjunctiva were observed in the white light of the slit lamp. Some dots were stained red others blue or green. To be able to distinguish between a pure green colour (due to lissamine green) and blue (due to both lissamine green and rose bengal) the stained region was inspected in light filtered through the green slit lamp filter. If the dot disappeared (merged into the green environment) it had been stained by lissamine green alone. If still visible as a black dot on the greenish background it was blue thus having also been stained by rose bengal.

The staining i.e. colour (green blue or red) grade and location was entered on a diagram for each individual case.

The grading is arbitrary ranging from 1 to 5 grade 1 representing minimum staining grade 3 moderate and grade 5 maximum.

Slit Lamp Examination

Lissamine green is useful for vital staining of cornea and conjunctiva punctate green staining being noticed often.

Table I
101 eyes vital stained by lissamine green

Normal	64
Keratitis	29
Corneal graft	4
Contact lens	4
Erosion of cornea	11
Corrosion of cornea	4
Infect conjunctivitis	17
Simple chron conj	11
Conj sicca	9
Cat extr (< 14 days)	9
Entropion	5
Other cases	11

Marx line on the conjunctiva along the lid margin is always stained. Corneal erosion and keratitis are stained to satisfaction.

When lissamine green and rose bengal are mixed or instilled successively the blue colour predominates that is the regions concerned are stained by both lissamine green and rose bengal. However we often find dots stained only green or only red.

Green most often predominates over red when lissamine green is instilled before rose bengal or a mixture of the two dyes is used (Fig 2).

The blue lissamine green rose bengal mixture preserves the specific staining properties of the two components the mixture being able to stain a pure red colour or a pure green colour as well as blue.

By staining first with rose bengal and next with lissamine green the red colour seems to predominate over the green (Fig 3).

In other words when the two dyes are instilled successively the first one instilled seems to dominate the picture.

Using a mixture of the three dyes lissamine green rose bengal and fluorescein the green component will be suppressed (Fig 4). This is presumably due to fluorescein destroying the green component. Conforming to this the mixture will gradually grow brown. On subsequent staining of the same eye without use of fluorescein the green colour will predominate again.

The stable blue mixture of lissamine green and rose bengal without fluorescein must be supposed to give the most correct picture of the relation

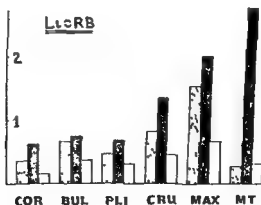


Fig 2

Lissamine green - rose bengal mixture. Viral staining of different conjunctival and corneal regions. Arbitrary gradings from 1 to 2. Dotted columns green (lissamine green) black columns blue (lissamine green and rose bengal) non coloured columns red (stained by rose bengal alone).

Vital Staining by Lissamine Green

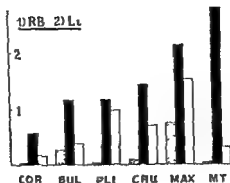


Fig 3

Vital staining first with rose bengal and next with lissamine green Cf Fig 2

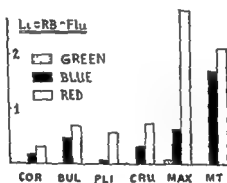


Fig 4

Mixture of lissamine green, rose bengal and fluorescein Vital staining of cornea and conjunctiva Cf Fig 2

between the two components 1% lissamine green stains as well as or rather slightly better than 1% rose bengal (Fig 2)

A study of the different diagnostic groups showed lissamine green to be as efficient as rose bengal for diagnosing pathological processes e.g. corrosion (slaked lime HNO_3 or NaOH) keratitis (dendritic zosteroid marginal and central) traces of pressing contact lens keratoconjunctivitis sicca etc

In corneal erosion epithelial discontinuity is stained distinctly by fluorescein but not always by rose bengal or lissamine green

In a case of mild dendritic keratitis the dendriform pattern was stained a

weak green and blue by the lissamine green rose bengal mixture (grade 1 of both) Subsequent staining with 10% rose bengal gave pronounced red staining (grade 4) of the pattern

Thirty one eyes were studied closely with a view to the sites of the colorations of Marx line Blue dominated in most cases Red occurred most often medially

(In 16 eyes red predominated medially, green laterally and blue between these regions In six the red colour was localized anteriorly and the green posteriorly in Marx line In eight eyes red blue and green dots were mingled irregularly In one eye Marx line was red medially in the lower lid but laterally in the upper)

The green and the red dots were seen to fade at equal rates the colour within the vital staining regions having thus subsided within from 30 min to a few hours Permanent vital staining (tattooing) has never been observed after staining with lissamine green not even in cases of deep corrosion with exposed connective tissue

Microscopy

Lissamine green stains degenerate cells dead cells and mucous fibrils in the same manner as does rose bengal

The cell nucleus is generally stained more intensely than the cytoplasm Vacuoles in the mucous thread remain unstained

In 77 cases the mucous thread was transferred to a slide after vital staining with lissamine green and rose bengal The transfer was performed cautiously from the inferior conjunctival fornix between two wooden sticks The mucous thread was kept in a moist chamber until drops of isotonic neutral phosphate buffer were applied The specimen was then covered by a cover slip and subjected to microscopy

In response to the vital staining the mucous thread assumed a blue colour in some zones and a green or red in others The differently stained zones alternated irregularly along the entire length of the thread Thus for instance four or five large blue zones might be seen together with two or three green and some smaller red zones

Within the individual zone all elements were of the same colour The nucleus was seen to be more intensely stained than the cytoplasm but the shade was the same Mucous fibrils had the same colour as the neighbouring cells Staining was noticed in all kinds of epithelial cells and leucocytes

Table II

The percentage areas of the mucous thread stained green blue or red by lissamine green (L) and rose bengal (RB) respectively using different techniques SEM given for the L:RB mixture

	Green	Blue	Red	No
L:RB mixt	20.1 ± 4.3	10.5 ± 4.2	9.3 ± 2.2	59
1) L 2) RB	99.7	61.7	16.1	19
1) RB 2) L	8.8	64.7	96.4	19

Table II illustrates the sizes of the green blue and red mucous thread areas respectively. Most of the thread (60-70 per cent) becomes blue i.e. is stained by both lissamine green and rose bengal. Smaller areas become stained by one component only. On staining with the two dyes mixed or successively using lissamine green first the green component will predominate over the red. Conversely red will predominate over green if rose bengal is applied first.

This observation harmonizes with the result of the slit lamp examination. The primarily instilled dye predominates over the secondarily instilled one. When mixed lissamine green predominates over rose bengal.

In 22 cases I studied epithelial scrapings from Marx line or cells from conjunctival fluid sucked up with a pipette after vital staining.

Scrapings from Marx line consist of non stained epithelial flakes among which are found islets of stained cells corresponding to the coloured dots seen in the slit lamp. After staining with the lissamine green rose bengal mixture alternating totally green and totally red cell islets were seen.

The cells in the conjunctival fluid may be red blue green or unstained. The granules of neutrophilic leucocytes always have the same shade of colour as the nucleus and cytoplasm of the cell concerned.

Trypan blue stains exclusively dead cells. Successive staining with trypan blue and lissamine green gives many green cells but only few blue ones. In other words lissamine green stains not only dead cells but also less damaged degenerate cells.

Sudanite tetrazolium yields a red colour to enzyme containing granules in the cell cytoplasm. On successive staining with tetrazolium and lissamine green the following cell categories were seen: 1) unstained cells 2) cells with red granules 3) green cells with red granules and 4) green cells with no granules.

These categories may be characterized as follows 1) live cells 2) mildly damaged cells with enzyme activity 3) more degenerate cells with enzyme activity 4) highly degenerate or dead cells with no enzyme activity

DISCUSSION

The present investigation showed lissamine green to be useful for vital staining the cornea and the conjunctiva. No side effects have been detected.

Lissamine green stains degenerate cells, dead cells and mucus, thus having the same vital staining properties as rose bengal and various other dyes staining less intensely than rose bengal (eosin, merbromine, scarlet red, Bismarck brown).

Using vital stains having different properties, specific staining is obtained in the preparation for microscopy (blue mucus and red cells on vital staining with trypan blue and rose bengal; blue nuclei and red cytoplasm on vital staining with trypan blue and rose bengal).

Using the closely related dyes lissamine green and rose bengal, no such differentiation is obtained, cells and mucus being of the same colour in alternating zones.

Staining with lissamine green and rose bengal has the advantage that it is possible to distinguish between staining by either component separately (green or red) and staining by both components (blue) by means of a green filter.

Slit lamp examination and measurement in the microscope showed that in successive vital staining the first dye applied stains more intensely than the next one. This renders comparison between the two dyes difficult.

Use of a dye mixture eliminates this disadvantage. However, if the components of the dye mixture influence each other, the result achieved will be false. This was noticed to be true of the mixture of fluoresceine, rose bengal and lissamine green, where the latter was suppressed. The mixture without fluoresceine, on the other hand, was likely to give a correct picture of the staining properties of lissamine green in relation to those of rose bengal.

The results of the investigation go to show that 1% lissamine green stains a little more intensely than 1% rose bengal.

The most pronounced vital staining is obtainable with 10% rose bengal (Norn 1970). The 10% concentration stains not only dead cells and moderately degenerate cells, but also slightly degenerate cells. These latter cells are hardly stainable by lissamine green, this dye being less water soluble than rose bengal. Lissamine green is hardly employable in concentrations above 2%.

Does lissamine green then have any advantage over other dyes for vital staining cornea and conjunctiva?

A green dye may be used where this colour might be preferable instead of the red rose bengal with almost identical vital staining results

Green is more distinctly visible than red on a reddish background. The staining is seen plainly on the conjunctiva but less so on the cornea

A green dye is suitable for double staining with red dyes. In testing red dyes with hitherto unknown vital staining properties lissamine green will be suitable for comparison (e.g. alizarin, safranin, trypan red, Congo red, neutral red).

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INTRAORBITAL VALVE FRACTURE

BY

ANDERS BORTHNE

A blow out fracture with a posteriorly hinged fragment in the orbital floor was found to create a valve mechanism when subperiosteal retraction was exerted on the orbital content for inspection of the fracture site. The valve mechanism which locked a part of the prolapse in the antrum was due to a movable and depressed fragment which hooked the overriding herniated soft tissues with its free edge. A traction on the inferior rectus muscle similar to a forced deduction test was demonstrated to have the same valve closing effect. The surgical problem was solved by freeing the prolapse from the fragment edge in the antrum and keeping the valve open on retraction. This could be carried out without tearing the tissues by means of simple malleable instruments that were at hand.

Key words: orbit - blow out fracture - trap door fracture - orbital fracture - surgery of orbital fracture

The surgical treatment of blow out fractures is directed primarily toward freeing of herniated tissues and restoration of the orbital configuration. A direct orbital approach often gives the best exposure of the fracture site and the involved orbital structures.

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A fracture found in the orbital floor of a nine year old boy however gave an unusual problem when the herniated orbital tissues were to be replaced. This was because of a valve mechanism in the maxillary sinus. Although of a simple mechanical nature this was not obvious at first and it needed special surgical treatment.

The purpose of this paper is to describe the fracture and to detail the surgical technique which made an additional antral approach unnecessary.

Case Report

A 9 year old boy struck the left side of his face when skiing. He was seen by us the day after on October 12th 1971. There was a small cut below the inferior orbital rim and moderate hematoma in the eyelids (Fig 1). The orbital rim was intact and there was neither infraorbital hypoesthesia nor enophthalmus. On upward gaze diplopia and reduced motility of the left globe appeared. A traction test gave the impression of mechanical impediment of the inferior rectus muscle. The Hess Chart (Fig 2) showed that both inferior rectus and inferior oblique were involved. A pre operative X ray tomography (Fig 3) showed a blow out fracture of the floor of the left orbit. The fourth day after the accident there was slight enophthalmus on the left side.

The patient was operated on the 5th day by a direct orbital approach. Orbital tissue filled the fracture hole and was partly locked in the antrum by a posteriorly hinged and deeply depressed solenoid fragment. By a special surgical technique the prolapsed tissues were gently freed without loss of fat. The fragment was reduced and fixed thus restoring the orbital floor.



Fig 1



Fig 2

Pre operative appearance on the 3rd day after the trauma. There is incipient enophthalmus on the left side. Eye movements showed signs compatible with mechanical impediment on left inferior rectus and left inferior oblique. The Hess Chart is shown in Fig 2.



Fig 3

Tomogram of the fracture showing a rounded density (arrowed) protruding into the maxillary air space from the nasal roof

Examination 12 months after the operation showed the eye to be normal Vision Maddox rod test and Hess Chart were normal The field of binocular single vision is shown in Fig 4

The Valve Mechanism

The prolapsed orbital tissue was mobile in relation to the fracture hole (Fig 3) and could easily be reduced to a certain extent both by traction on the

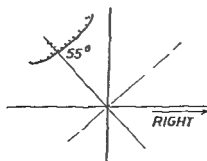


Fig 4

The field of binocular single vision 12 months after surgery show I/R diplopia (hatched) in a small area bordering on normal

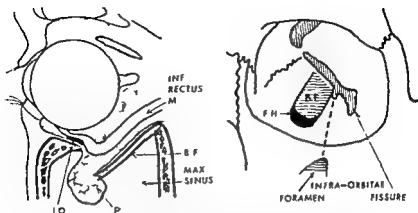


Fig 5

Left A section running through the orbit and the maxillary sinus in the vertical plane showing the valve fracture - Right Sketch of the left fractured orbit in frontal view

P Prolapsed orbital tissues B F Bone fragment

IO Inferior oblique muscle F H Fracture hole

inferior rectus muscle and by subperiosteal retraction of the orbital content. The lower part of the prolapse however became locked in the maxillary sinus when about half of it was reduced to the orbital side (Fig 6).

By placing a thin lachrymal probe beside the prolapse one detected the mobile bony fragment which proved to adhere to the prolapse when this was drawn upward and slipped as easily down again with the prolapse about one centimeter. The fragment sloped to the infraorbital fissure where it was hinged. The herniated tissues rode over the sharp bony fragment and when repositioning was attempted the prolapse was pinched between the edges of the fragment and the fracture hole.

Surgical Technique

When the subperiosteal retractor was lowered enough to open the valve the exposure of the fracture site was reduced to a narrow opening. In the next step which was to free the prolapse without tearing it a malleable Uchermann probe seemed useful. The flat budding end of it was bent to reach the anterior edge of the fragment. The prolapse which was hanging without drag in the antrum could then be pushed free from the fragment edge (Fig 7). The



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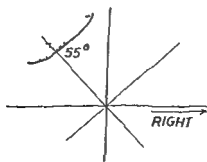


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There was no haematoma nor strangulation of the prolapse and it was not found necessary to open the reticulated structures for inspection of the muscles as the lobulated surface was intact

The fragment which by now was seen hanging down in the antrum anteriorly was freely movable at the hinge. The Uchermann probe was bent to a hook which was used to elevate the fragment. This was next luxated to the orbital side of the fracture hole where it lay steady (Fig 7). As the posterior part of the fragment held a certain pressure it was found expedient to fixate the fragment. Holes for the sutures were made with an ordinary dentist's drill and the fragment was fastened with two sutures of supramid.

Discussion

While reconstruction of orbital floor defects now can be done in many different ways depending somewhat on the circumstances there is only one way to treat the soft tissue prolapse. It must be replaced into the orbit in the gentlest way possible. It is therefore of interest to concentrate on the mechanisms directly concerning this part of the operation.

From this point of view it should be clear from the foregoing that the valve mechanism is an essential feature of this fracture. I suggest 'intraorbital valve fracture' as a suitable name. This name not only indicates a causal trap door mechanism but specifies also the valve obstacle which is of great surgical importance.

When an 'open trap door' fracture is found on the radiogram (Fueger & Milauskas 1969) the valve mechanism should be suspected although this finding indicates only one of the conditions necessary.

The valve mechanism became active for the following reasons. There was a hinged and deeply depressed bone fragment (an 'open trap door' fracture); the fragment was movable at the hinge and the prolapse was riding over the fragment edge in such a way that this edge hooked the soft tissues. These are the conditions.

The mere traction on the inferior rectus muscle or a lifting of the orbital content with a retractor underneath the periorbita for inspection of the fracture site activated the closing movement of the valve.

Freeing of herniated tissues is usually easily effected by a hand over hand technique using two blunt elevators while an assistant holds the retractor. In this case it is possible that this ordinary technique could have jammed the prolapse and fixed the fragment in a normal or near normal position or tearing could have occurred or both (see Fig 6 R).

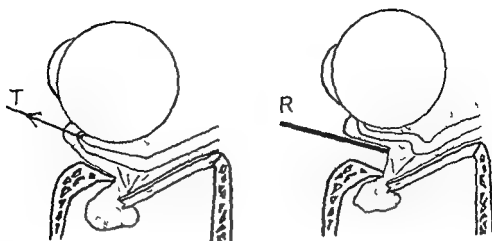


Fig 6

The valve mechanism shown in vertical section through the fracture. Traction on the inferior rectus (T) similar to a forced deduction test and subperiosteal retraction of the orbital content (R) for inspection of the fracture site made the valve tend to close. Note that the prolapse is pinched between the edges of fragment and fracture hole.

herniated tissues were then reduced partly by traction on the inferior rectus and partly by a hand over hand technique using the retractor and a blunt elevator.

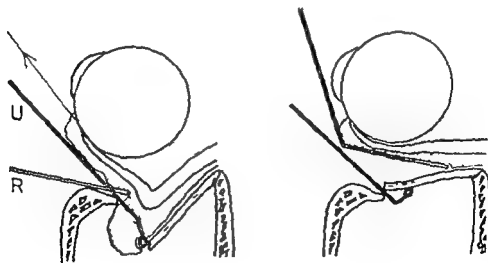


Fig 7

Left: The prolapse was freed from the fragment edge by using the bent budding end of an Uchermann probe (U) and a subperiosteal retractor (R) - Right: The bone fragment luxated to the orbital side of the fracture hole where it was fixed by suturing.

There was no haematoma nor strangulation of the prolapse and it was not found necessary to open the reticulated structures for inspection of the muscles as the lobulated surface was intact

The fragment which by now was seen hanging down in the antrum anteriorly was freely movable at the hinge. The Uchermann probe was bent to a hook which was used to elevate the fragment. This was next luxated to the orbital side of the fracture hole where it lay steady (Fig 7). As the posterior part of the fragment held a certain pressure it was found expedient to fixate the fragment. Holes for the sutures were made with an ordinary dentist's drill and the fragment was fastened with two sutures of supramid.

DISCUSSION

While reconstruction of orbital floor defects now can be done in many different ways depending somewhat on the circumstances there is only one way to treat the soft tissue prolapse. It must be replaced into the orbit in the gentlest way possible. It is therefore of interest to concentrate on the mechanisms directly concerning this part of the operation.

From this point of view it should be clear from the foregoing that the valve mechanism is an essential feature of this fracture. I suggest *intraorbital valve fracture* as a suitable name. This name not only indicates a causal trap door mechanism but specifies also the valve obstacle which is of great surgical importance.

When an open trap door fracture is found on the radiogram (Fueger & Vitlauskas 1969) the valve mechanism should be suspected although this finding indicates only one of the conditions necessary.

The valve mechanism became active for the following reasons. There was a hinged and deeply depressed bone fragment (an open trap door fracture) the fragment was movable at the hinge and the prolapse was riding over the fragment edge in such a way that this edge hooked the soft tissues. These are the conditions.

The mere traction on the inferior rectus muscle or a lifting of the orbital content with a retractor underneath the periorbita for inspection of the fracture site activated the closing movement of the valve.

Freeing of herniated tissues is usually easily effected by a hand over hand technique using two blunt elevators while an assistant holds the retractor. In this case it is possible that this ordinary technique could have jammed the prolapse and fixed the fragment in a normal or near normal position or tearing could have occurred or both (see Fig 6 R).

Loss of orbital fat to the antrum and outflowing of fat in the operation field make the operation much more troublesome and will invariably lead to complications. With this in mind there is also reason to issue a word of warning regarding the forced deduction test. If this diagnostic test is necessary it should be carried out carefully owing to the risk of tearing the connective tissue that surrounds the fat (see Fig 6'T).

This method is probably of value if the surgeons are prepared to meet the intraorbital valve problem as described. The nature of the valve mechanism is very simple and I feel sure that it will appear again either in this pure form or in combination with other trapping mechanisms.

Reference

- Fueger G F & Milauskas A T (1969) Two new radiographic projections and a modification of orbitography in the diagnosis of orbital blow out injuries II Results *Symposium on Orbital Fractures* Amsterdam 1969 Internat congress series No 216 ISBN 90 219 0162 5 *Excerpta Medica* Amsterdam 1970 pp 45-64

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EXPERIMENTAL ULTRASONIC EXAMINATIONS OF INTRAOCULAR INTRASCLERAL AND RETROBULBAR FOREIGN BODIES

BY

JON S. LARSEN and SVEN T. GJERULDSSEN

Normal human eyes removed at autopsy with the total orbital contents were used for ultrasonographic examinations of intravitreal, intrascleral, retrobulbar and intraorbital foreign bodies. These were of various sizes and materials: iron, brass, aluminium, copper, glass, plastic (polystyrene), stone (slate), cement and wood (oak), and all could be demonstrated by ultrasonography. The smallest intravitreal foreign body (of iron) measured approximately $0.2 \times 0.15 \times 0.1$ mm, the smallest intrascleral (of iron) $0.5 \times 0.4 \times 0.2$ mm and the smallest retrobulbar (of iron) $0.7 \times 0.5 \times 0.3$ mm. Foreign bodies in the orbit were much more difficult to detect and had to be larger to allow proper demonstration by ultrasonography.

Key words: ultrasound - ocular foreign bodies

In 1939 Oksala reported that intraocular foreign bodies could be detected by ultrasonographic examinations, and in the following years several studies confirmed the value of this method in diagnosis of foreign bodies (Oksala & Lehtinen 1939, Oksala, Nover & Stallkamp 1960, 1962, Vanysek et al 1962, Vanysek et al 1965, Oksala & Salminen 1965, Gernet & Hennewig 1966).

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cylinder and searching for the foreign body was started by holding the transducer directly in contact with the sclera in the pars plana area. This position of the transducer was used not only for the eyes with removed anterior segment but also for the intact eyes. Special attention was paid to the problems of demonstrating foreign bodies lying on the retina. From the series of intra vitreal foreign bodies two of the smaller ones were selected and these were placed intravitreally in direct contact with the retina. The foreign bodies could then be localized in the usual manner by getting the transducer into touch with the sclera. However to obtain an optimal echo the transducer was also immersed into the corpus vitreum in a position perpendicular to the foreign body. All retroscleral and intraorbital foreign bodies were registered from at least 4 different directions. The echograms were recorded photographically by a Polaroid oscilloscope camera using the Kretztechnik system and Polaroid I and Film Type 107.

Table I
Weight of foreign body in mg

Type of foreign body	No. intravitreal		No. intrascleral		No. retroscleral		No. intraorbital	
Iron	1	0.490	01	1.159	23	3.191	39	33.969
	2	0.914	22	0.334	26	0.691	40	8.399
	3	0.135						
	4	00.0						
	5	00.3						
Brass	6	13.0	03	3.16	07	1.836	41	01.534
	7	0.419	04	4.711	23	0.130	47	11.968
Aluminium	8	0.139			09	1.609		
	9	0.078			30	0.319		
Copper	10	1.590						
	11	0.673						
Glass	12	0.037			31	1.975	43	6.000
	13	00.1			32	1.705		
Plastic	14	0.163			33	2.351	44	1.43
	15	0.104			34	0.891		
Stone	16	0.736			35	9.353	45	6.010
	17	0.119			36	0.163		
Cement	18	0.453			37	1.719		
	19	0.01						
Wood	20	0.1			38	0.337	46	2.850

Divergent opinions exist regarding the possibilities of ultrasonic detection of foreign bodies localized close to the bulbar wall or within the bulbar wall itself. It has been maintained that only large foreign bodies with this localization could be detected and small foreign bodies not at all (Nover & Strillkamp 1962, Oksala & Salminen 1966, Runyan & Penner 1969, Coleman & Trokel 1971). On the other hand Ossoinig & Scher (1969) reported that foreign bodies impacted within the bulbar wall or localized in its immediate vicinity could be diagnosed by ultrasonographic examinations.

It is clear that various types of ultrasonic equipment may give widely different results. Using a new model echo ophthalmograph the purpose of this investigation was experimentally to determine if and how intravitreal intra-scleral and retrobulbar foreign bodies of various sizes and materials could be detected and properly localized with this modern equipment.

Material and Methods

The apparatus used in the investigation was the Kretztechnik ultrasonograph model 7200 MA with an 8 Mc/5 mm (NM 8-5 k) transducer. Normal human eyes obtained at autopsy the first day post mortem were used in the investigation. The eyes were removed together with the total orbital contents including optic nerve, muscles and orbital fat. The preparation was kept in a moist chamber at +4°C until it was used in the examinations, usually within a few hours.

A total of 36 intravitreal foreign bodies consisting of iron, brass, aluminium, copper, glass, plastic (polystyrene), stone (slate) and wood (oak) were prepared in various sizes. In addition to the above mentioned 8 intrascleral foreign bodies were made consisting of iron and brass and 23 retroscleral foreign bodies of iron, brass, aluminium, glass, plastic (polystyrene), stone (slate) and wood (oak) and also 14 intraorbital foreign bodies of iron, brass, plastic (polystyrene), stone (slate) and wood (oak).

To get the foreign bodies properly placed intravitreally, the anterior segment of the eye including cornea, iris and lens had to be carefully removed. Intact eyes were used for the intrascleral, retroscleral and intraorbital foreign bodies. A small incision was made near the posterior pole and the foreign body introduced into a little scleral pocket. The retroscleral foreign bodies were placed near to the sclera at the posterior pole with a liberal amount of the orbital contents behind. The intraorbital foreign bodies were buried in the orbital fat at various depths. The preparation was brought into a conical metal

From a total of 81 foreign bodies examined a positive echogram in all cases was obtained with a distinct foreign body echo permitting a proper diagnosis and localization. For practical reasons only 46 of these echograms are reproduced. The corresponding foreign bodies were numbered 1-46 and weighed (Feinwage Type 1801 Sartorius - Werke A/G) the results are given in Table I. The foreign bodies were then mounted on paper and x ray and black and white photographs were taken (Fig. 1).

Results

Intravitreal

The foreign bodies of metal except of aluminium appeared clearly in the x ray photograph (Fig. 1). The nonmetallic foreign bodies were not shown in the roentgenogram except the greatest of glass (No. 12) and the foreign bodies of cement (Nos. 18 and 19) which gave a fairly distinct x ray shadow.

The ultrasonic picture of the metallic foreign bodies (Nos. 1-11) is shown in Fig. 2 and that of the nonmetallic ones (Nos. 12-20) in Fig. 3. All foreign bodies both the metallic as well as the nonmetallic gave high and distinct echo spikes even with moderate decibel (db) intensities. This also applied to the smallest of both types No. 5 (iron) and No. 13 (glass). The foreign bodies lying on the retina could be detected by holding the transducer in contact with the sclera but a more illustrative echogram from the foreign body and the posterior wall structures could be obtained when the transducer was placed intravitreally in a position perpendicularly to the foreign body (Fig. 4).

Intrascleral

The intrascleral foreign bodies of iron and brass (Nos. 21-24) (Fig. 1) were in the size order 0.934-5.167 mg. and could without serious difficulties be found and properly localized as intrascleral (Fig. 5). Their optimal echo spikes were higher than those from the sclera. A clearly 3-topper echo with spikes from the anterior scleral wall, the foreign body and the posterior scleral wall was obtained only when the echo giving surfaces of the sclera and the foreign body approximately were in planes hit perpendicularly by the ultrasound beam. We always tried to get an optimal echo both from the foreign body and from the sclera. Occasionally this could be obtained only by tilting of the transducer which resulted in rather low echoes from the rest of the orbital contents.

Localization of foreign body	Type of foreign body									
	Iron	Brass	Aluminum	Copper	Glass	Plastic	Stone	Cement	Wood	+
Intravitreal	1-5	6 7	8-9	10-11	12 13	14-15	16-17	18-19	20	
Intrascleral	21-22	23 24								
Retroscleral	25 26	27 28	29-30		31-32	33-34	35-36	37	38	
Intraorbital	39 40	41-42			43	44	45		46	



O polystyrene slit + oak

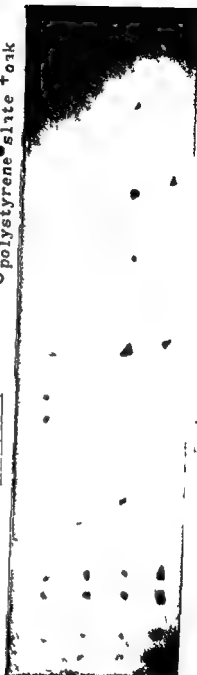


Fig. 1

Photograph and roentgenogram of the foreign bodies. Both parts of the figure in scale 1:1. The foreign bodies are numbered in succession 1-46.

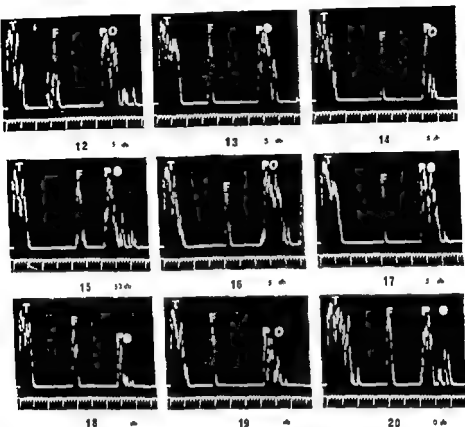


Fig 3

Ultrasonograms showing the intravitreal nonmetallic foreign body as T = transmitter pulse F = foreign body P = posterior bulbar wall O = orbital tissue

Retrocleral

The retrocleral foreign bodies (Fig 1 Nos 25-33) were made in size orders pertinent for that localization the material of the foreign bodies being taken into account. These rather large foreign bodies were often characterized by a two topped or a multi topped echo. It was considered important to get optimal echoes both from the foreign body and from the sclera. Relatively low echoes from the orbital tissue resulted when the transducer had to be tilted. The lightest of the metallic foreign bodies consisted of aluminium and weighed 0.310 mg (No 30) while the lightest nonmetallic bodies consisted of stone (slate) and weighed 0.168 mg (No 36). Like the other retrocleral foreign bodies

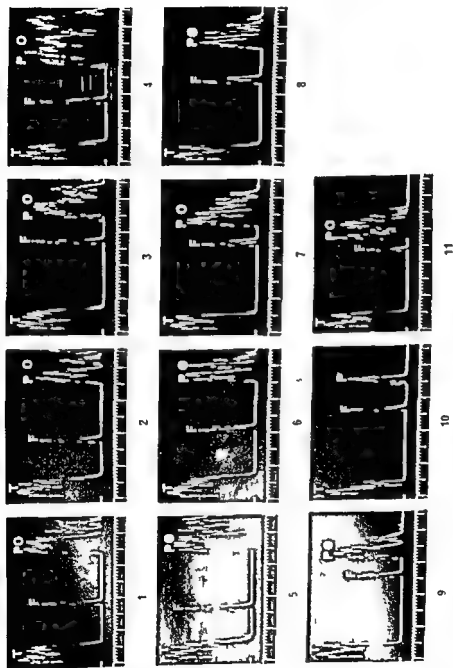


Fig 2

Ultrasonograms showing the intravital metallic foreign bodies T = transmitter pulse F = foreign body P = posterior bulbar wall O = orbital tissue The number of these and the following ultrasonograms refer to the respective foreign body number in Fig 1

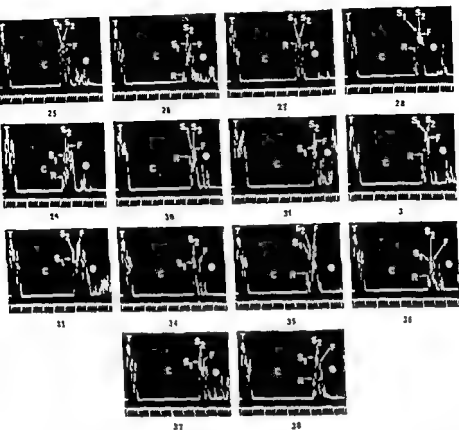


Fig 6

Ultrason grams showing the retrolschleral foreign bodies T = transmitter pulse C = vitreous R = retina S_1 = anterior scleral wall S_2 = posterior scleral wall F = foreign body O = orbital tissue

included in the examination these small foreign bodies also produced a distinct echo immediately behind the scleral complex (Fig 6)

Orbital

Even though the orbital foreign bodies were large (1.48-35.969 mg) they were more difficult to detect with certainty than the intravitreal intrascleral and retrolschleral foreign bodies. In the first place this was due to the tendency of the orbital contents in some positions of the transducer to give an echo of equal amplitude as that of the foreign body. To exclude a false foreign body

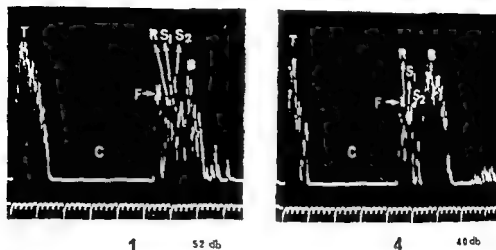


Fig 4

Ultrasonograms showing foreign bodies lying on the retina (Nos 1 and 4 in Fig 1). The transducer is here placed in the vitreous after removal of the anterior segment of the eye. T = transmitter pulse C = vitreous F = foreign body R = retina S_1 = anterior scleral wall S = posterior scleral wall B = retrobulbar tissue

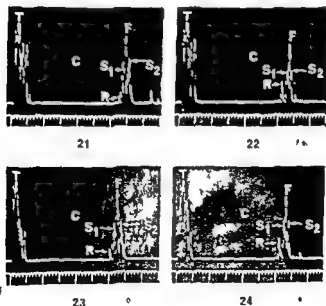


Fig 5

Ultrasonograms of the intrascleral foreign bodies T = transmitter pulse C = vitreous R = retina S_1 = anterior scleral wall F = foreign body S = posterior scleral wall

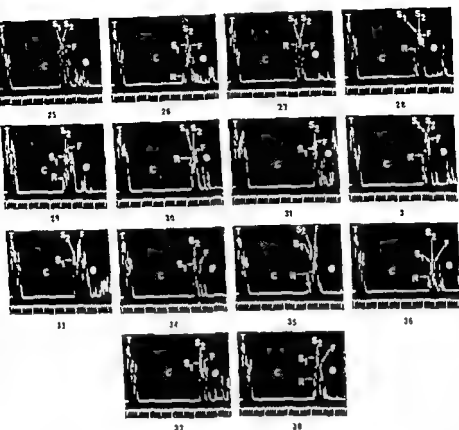


Fig 6

Ultrasonograms showing the retro scleral foreign bodies T = transmitter pulse C = vitreous R = retina S_1 = anterior scleral wall S_2 = posterior scleral wall F = foreign body O = orbital tissue

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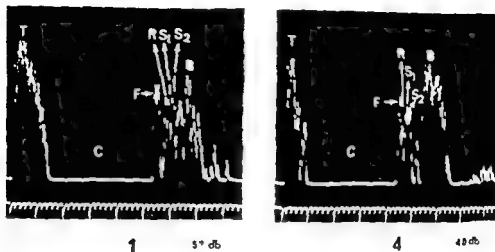


Fig 4

Ultrasonograms showing foreign bodies lying on the retina (Nos 1 and 4 in Fig 1). The transducer is here placed in the vitreous after removal of the anterior segment of the eye. T = transmitter pulse C = vitreous F = foreign body R = retina S₁ = anterior scleral wall S = posterior scleral wall B = retrobulbar tissue

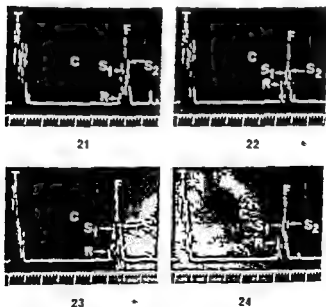


Fig 5

Ultrasonograms of the intrascleral foreign bodies. T = transmitter pulse C = vitreous R = retina S₁ = anterior scleral wall F = foreign body S = posterior scleral wall

echo demonstrations in at least 4 different meridians were made of all orbital foreign bodies in this series prior to photographic registration (Fig 7)

Discussion

Intra as well as extrabulbar foreign bodies could in this experimental investigation be detected and properly localized in relation to the posterior wall structures of the eye. The results however cannot be directly compared to actual foreign body examinations *in vivo*. A static echogram is produced while an *in vivo* examination would give a dynamic echogram on account of pulsations in the orbit and micro movements of the eye. The interpretation of the findings would then be more difficult especially for localizations other than the corpus vitreum.

Experimentally small and large foreign bodies of the same form and material give distinctly different echo amplitudes. Using the same db intensity higher echoes were obtained from a steel disc of 2 mm diameter than from a steel disc of 1 mm diameter (Vanysek et al 1970). In practical ophthalmology however foreign bodies usually have irregular polygonal forms often similar to those shown in Fig 1. Under these circumstances the echoes vary in accordance with the echo giving surfaces. For this reason it is difficult to establish any relation between the size of a foreign body and the height of its echo. An ultrasonic determination of the real size of a foreign body therefore seems impossible as indicated in Fig 2 by the almost identical echoes from the foreign bodies No 1 (iron) weight 0.480 mg and No 2 (iron) weight 0.214 mg. Sometimes however an impression may be gained of dealing with either a small or a large foreign body. A small foreign body most frequently would give a narrow single topped echo as shown in Fig 2 Nos 1-5 (iron) and in Fig 3 Nos 17 (stone) and 19 (cement). On the other hand a broad two or multi topped echo complex most likely could be ascribed to a large foreign body (Fig 5 Nos 29, 35 and 37).

The various materials of the foreign bodies examined had no specific and characteristic echogram. They all gave strong echoes which is shown in Fig 2 Nos 1 (iron) C (brass) ■ (aluminium) and in Fig 3 Nos 14 (plastic) 18 (stone) and 19 (cement). Thus a qualitative evaluation of the foreign body material seemed impossible. This conclusion is in accordance with the findings of Nover & Stallkamp (1967).

The smallest intravitreal foreign body consisted of iron (No 5). Division of its weight 0.073 mg by the specific gravity of iron $\sim 7.8 \text{ g/cm}^3$ gave a volume of 0.009 mm³ which would correspond to a piece of iron approximately measuring $0.2 \times 0.15 \times 0.1 \text{ mm}$ which again were roughly the measures of the

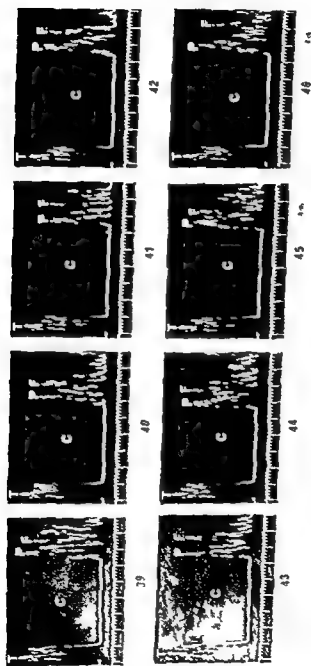


Fig 7
 Ultrasonograms of the intraorbital foreign bodies I = transmitter pulse C = vitreous
 P = posterior bulb/wall I = foreign body

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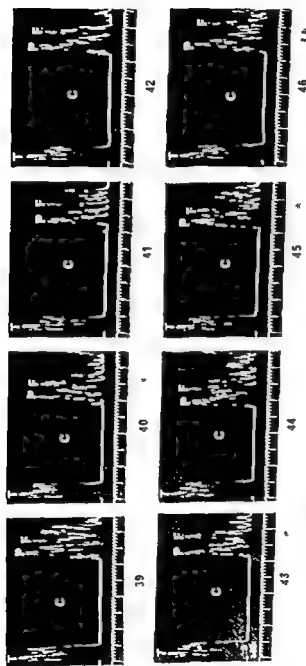


Fig 7
Ultrasonograms of the intraorbital foreign bodies T = transmitter pulse C = vitreous
P = posterior bulbar wall F = foreign body

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actual foreign body. The smallest nonmetallic foreign body (No. 13) consisted of glass. Its weight was 0.054 mg; by calculation the specific gravity was 3.5 g/cm³ and the volume 0.0154 mm³, which would correspond to a piece of glass approximately measuring 0.25 × 0.25 × 0.25 mm. Distinct high amplitude echoes were obtained from all the foreign bodies in this group, even the smallest ones (Table I). It seemed to be confirmed that intravitreal foreign bodies consisting of iron, brass, aluminium, copper, glass, plastic, stone, cement or wood could be detected by ultrasonography also when they were much smaller than what usually would be required to pass through the cornea/sclera barrier.

By experimental investigations Nover & Stallkamp (1962) and Okamoto & Salminen (1966) found that a foreign body had to be separated from the posterior bulbar wall by 1–2 mm to give a separate echo. The present series of examinations, however, showed that foreign bodies lying directly on the retina could be clearly detected by ultrasonography provided that overloaded echoes were not produced. By lowering the db intensity the respective echoes could be differentiated.

In the same manner an intrascleral foreign body could clearly be detected when the db intensity was lowered sufficiently (40–47) to make it possible to differentiate and separate the foreign body echo from the bulbar wall echoes. A retrolscleral foreign body echo could be differentiated from the echoes of the posterior bulbar wall and the orbital structures at db intensities about 42–50 db. The examined intra- and retrolscleral foreign bodies all produced stronger echoes than the sclera and the retrobulbar tissue structures respectively. The smallest intrascleral foreign body examined (No. 22) consisted of iron and measured approximately 0.5 × 0.4 × 0.2 mm and its weight was 0.394 mg, which would respond to a volume of 0.0424 mm³. This relatively small foreign body gave a distinct intrascleral echo (Fig. 5, No. 22) which showed that even a very small intrascleral foreign body could be detected by ultrasonography.

Experimentally the retrolscleral foreign bodies were revealed by a strong high amplitude echo behind the scleral complex (Fig. 6). Even the smallest one of metal (iron, No. 26) approximately measuring 0.7 × 0.5 × 0.25 mm, weighing 0.691 mg, and the smallest nonmetallic foreign body (No. 36) of stone (slate) approximately measuring 1.0 × 0.6 × 0.15 mm and weighing 0.168 mg, could be detected and localized retrolsclerally.

More difficult was the detection of an orbital foreign body. This was partly due to the absorbing effect of the orbital fat and partly to the high echoes from the orbital tissue itself, which often were hard to discriminate from the proper foreign body echo. To avoid misinterpretations of the echograms and also to secure the most accurate localization of the foreign body, its demonstration in several meridians was considered necessary.

that it was reduced no mention being made either of the number of cases to which this applied or whether these patients had retinopathy. To some of their patients whose light perception was impaired 60 000 units of caroten was given daily for 4 days. This resulted in a substantial increase in their blood caroten level but had no effect on dark adaptation. If they were given 60 000 units of vitamin A daily for 7 days dark adaptation improved but became again subnormal if vitamin A was discontinued. According to Brazer & Curtis (1939) this observation confirmed the view expressed by earlier investigators that some diabetics were unable to convert caroten to vitamin A. Nylund (1944) examined light perception in six diabetics and found it to be normal. Determination of the vitamin A concentration in the blood showed it to be normal. Escudero et al. (1941) determined the blood levels of caroten and vitamin A respectively in 20 diabetics and although they were high light perception was still impaired. Livingstone (1945) examined by scotometry a series of diabetics in whom there was no ophthalmoscopic evidence of fundal changes. This revealed small scattered scotomas in the central field of vision. He assumed that the scotomas represented localized anoxic areas in the retina basing his view on the observation made in earlier investigations that vascular changes in diabetics may not necessarily be visible through the ophthalmoscope.

This paper reports the observations made in a series of diabetics with retinopathy who were admitted to this department for treatment by photocoagulation in order to investigate (i) whether dark adaptation is consistently impaired in diabetic retinopathy and (ii) the effect of photocoagulation on dark adaptation. The adaptation curves were recorded before and after treatment in each case.

Case Material and Methods

This series included 20 diabetics the ages of 9 patients ranging from 20 to 40 years and of 11 patients from 40 to 60 years. The dark adaptation curves were recorded in all cases before and five to eighteen months after photocoagulation using the Coldmann Weekers adaptometer. The patients' visual acuity was good ranging from 0.6 to 1.0. With the exception of three cases in which retinopathy showed proliferative tendencies in the form of discrete patches of neovascularization in the plane of the retina the lesion was moderate and non-proliferative in character changes such as microaneurysms, punctate haemorrhages and exudates being present. The media were clear.

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PHOTOCOAGULATION IN DIABETIC RETINOPATHY WITH SPECIAL REFERENCE TO ITS EFFECT ON DARK ADAPTATION

BY

B ZETTERSTRÖM and M GJÖTTERBERG

The dark adaptation curves were recorded with the Coldmann Weckers adaptometer in 20 diabetics with retinopathy before and from five to eighteen months after photocoagulation. The ages of nine patients ranged from 20 to 40 years and of 11 patients from 40 to 60 years. No significant improvement or impairment of dark adaptation was observed after photocoagulation. In view of the fact that photocoagulation is used increasingly in the treatment of diabetic retinopathy this observation might be of some importance.

Key words: retina - diabetic retinopathy - dark adaptation - photocoagulation - oscillatory potentials

Many patients with diabetic retinopathy state that their ability to see in the dark is impaired despite the absence of objective evidence that their visual acuity is reduced. Only very few investigations of dark adaptation in diabetic retinopathy have been carried out and the reported results differ greatly. Feldman (1937) investigated dark adaptation in four diabetics and found it to be slightly subnormal in one and normal in the other three patients. Brazier & Curtis (1939) studied light perception in 20 juvenile diabetics. They reported

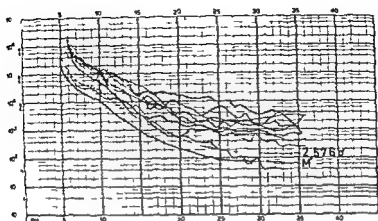


Fig 2

Dark adaptation curves recorded in the same age group as shown in Fig 1 after treatment by photocoagulation

For purposes of comparison Fig 1 shows the dark adaptation curves obtained in the nine patients in the age group 20-40 years together with the mean threshold values and the range of threshold values in healthy individuals of the same age range. It is seen that the appearance of the curves deviated from the norm in all cases in the former group thus indicating that dark adaptation was impaired in all these patients. No curve fell to the normal threshold level of 10×0.6 . The mean threshold value was calculated to be 10×0.7 log unit higher than normal in the 9 diabetics in this group. Fig 2 shows the appearances of the curves recorded five to eighteen months after photocoagulation. Only in one case did the curve show normal values. The mean threshold value was 10×0.9 . Figs 3 and 4 show the dark adaptation curves obtained from the eyes of the 11 patients in the age group 40-60 years before and from five to eighteen months after photocoagulation. The curves in this group were flatter than normal before as well as after treatment and therefore the values shown by the curves did not correspond to those normally obtained in this age group. The normal threshold level lies at 10. The mean values before and after photocoagulation were 10×0.8 and 10×0.9 respectively in the 11 patients in this group.

A careful study of the appearances of the curves before and after treatment in the individual cases in the age group 20-40 years showed that they had virtually the same appearances in four patients. In two patients the curves

Only one eye of each patient was treated and investigated. The apparatus used was the West German Zeiss photocoagulator producing 110 to 150 photocoagulation lesions each treatment using the 3° and 45° apertures. Only ophthalmoscopically visible changes in the fundus were treated i.e. discrete patches of neovascularization and microaneurysms with or without surrounding punctate haemorrhages. In the cases in which hard and yellow exudates resembling atoll formations were present only the microaneurysms situated in the centre of the atoll were coagulated and not the exudate itself. The visual fields were measured concurrently with the recording of the adaptation curves before and after treatment in all cases using the Goldmann perimeter.

Results

The dark adaptation curves recorded before photocoagulation were abnormal in all cases. Particularly towards the end of the time required for normal dark adaptation the curves were flatter than normal. After photocoagulation the curve dropped to the normal threshold value after 30 minutes in the dark in only one case.

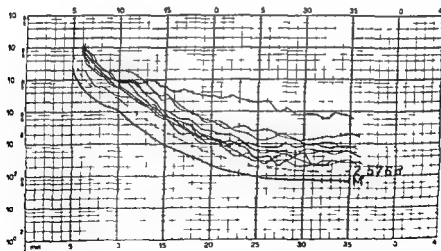


Fig 1

Dark adaptation curves recorded in nine diabetics between 20 and 40 years of age before photocoagulation. M: mean threshold values in healthy individuals in this age range. broken curve: upper borderline of the normal range of threshold values.

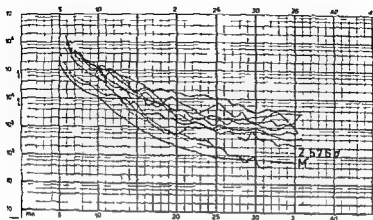


Fig 9

Dark adaptation curves recorded in the same age group as shown in Fig 1 after treatment by photocoagulation

For purposes of comparison Fig 1 shows the dark adaptation curves obtained in the nine patients in the age group 20-40 years together with the mean threshold values and the range of threshold values in healthy individuals of the same age range. It is seen that the appearance of the curves deviated from the norm in all cases in the former group thus indicating that dark adaptation was impaired in all these patients. No curve fell to the normal threshold level of $10^1 \times 0.6$. The mean threshold value was calculated to be $10^1 \times 0.7 \pm 1$ log unit higher than normal in the 9 diabetics in this group. Fig 9 shows the appearances of the curves recorded five to eighteen months after photocoagulation. Only in one case did the curve show normal values. The mean threshold value was $10^1 \times 0.9$. Figs 3 and 4 show the dark adaptation curves obtained from the eyes of the 11 patients in the age group 40-60 years before and from five to eighteen months after photocoagulation. The curves in this group were flatter than normal before as well as after treatment and therefore the values shown by the curves did not correspond to those normally obtained in this age group. The normal threshold level lies at 10. The mean values before and after photocoagulation were $10^1 \times 0.8$ and $10^1 \times 0.9$ respectively in the 11 patients in this group.

A careful study of the appearances of the curves before and after treatment in the individual cases in the age group 20-40 years showed that they had virtually the same appearances in four patients in two patients the curves

Only one eye of each patient was treated and investigated. The apparatus used was the West German Zeiss photocoagulator producing 110 to 130 photo coagulation lesions each treatment, using the 3° and 4.5° apertures. Only ophthalmoscopically visible changes in the fundus were treated i.e. discrete patches of neovascularization and microaneurysms with or without surrounding punctate haemorrhages. In the cases in which hard and yellow exudates resembling atoll formations were present only the microaneurysms situated in the centre of the atoll were coagulated and not the exudate itself. The visual fields were measured concurrently with the recording of the adaptation curves before and after treatment in all cases using the Goldmann perimeter.

Results

The dark adaptation curves recorded before photocoagulation were abnormal in all cases. Particularly towards the end of the time required for normal dark adaptation the curves were flatter than normal. After photocoagulation the curve dropped to the normal threshold value after 30 minutes in the dark in only one case.

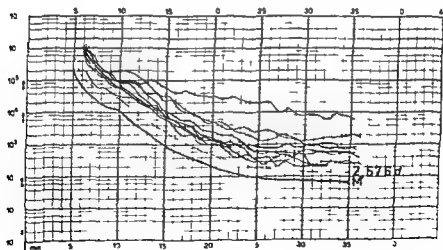


Fig 1

Dark adaptation curves recorded in nine diabetics between 20 and 40 years of age before photocoagulation. M: mean threshold values in healthy individuals in this age range. broken curve: upper borderline of the normal range of threshold values.

were lightly steeper than before treatment indicating improvement of dark adaptation in three patients they were slightly flatter after treatment indicating impairment of dark adaptation Of the 11 patients in the age group 40 to 60 years the appearances of the curves before and after treatment were virtually the same in 9 patients in one patient they showed that dark adaptation had slightly improved and in one patient that it had slightly deteriorated after photocoagulation

No relationship between the degree of severity of retinopathy and dark adaptation could be demonstrated nor was the effect of photocoagulation on retinopathy correlated with the ability to adapt to dark Broadly speaking the degree of severity of the retinopathy was virtually identical in all cases The follow up period was too short (five to eighteen months) to enable a fair assessment of the effect of photocoagulation to be made The retinal area coagulated was identical in size in each case each treatment producing from 110 to 130 photocoagulation lesions using the 3 and 4.5 apertures

No patient complained of subjective field loss in treated eyes The boundaries of the visual fields measured with the Goldmann perimeter concurrently with the recording of the dark adaptation curves before and after treatment were normal in all cases before treatment Of the 20 eyes treated slight defects of the visual field were recorded in nine eyes after treatment (Fig 5) In the

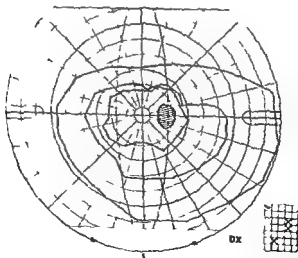


Fig 5

Visual field showing slight defects of a type recorded in nine of the 20 patients in this series after photocoagulation

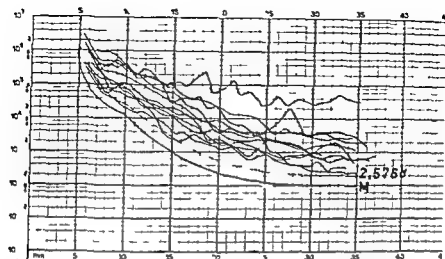


Fig 3

Dark adaptation curves recorded in 11 diabetics between 40 and 60 years of age before photocoagulation »M» mean threshold values in healthy individuals in this age range broken curve upper borderline of the normal range of threshold values

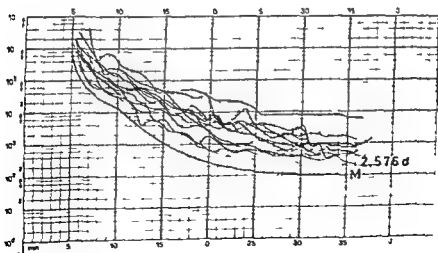


Fig 4

Dark adaptation curves recorded in the same age group as shown in Fig 3 after treatment by photocoagulation

photocoagulation were negligible. The possibility cannot be excluded that they were due either to errors in measurement or to differences in the conditions under which the patients were examined and therefore did not reflect the true situation.

In the cases of diabetic retinopathy associated with reduced dark adaptation discussed in this paper, no convincing evidence could be established that photocoagulation resulted in a further impairment of the ability of these patients to see in the dark. In view of the fact that photocoagulation is used widely in the treatment of diabetic retinopathy, this observation may be of some importance.

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other 11 eyes there was no evidence of field defects. There was no relationship between the defects of the visual field and the slight improvement or impairment of dark adaptation after photocoagulation.

Earlier investigations have shown that the electroretinogram (ERG) recorded by the standardized technique elaborated by Karpe (1945) is normal in diabetics with retinopathy of the same type as was present in the cases in this series (Karpe, Kornerup & Wulff 1958). François & De Rouck (1954) recorded the ERG in 36 diabetics with retinopathy and found it to be normal. This also applied to the cases in which retinopathy was in an advanced stage and numerous haemorrhages and exudates were present. In the present series an ERG was elicited by Karpe's technique in three patients before photocoagulation and was found to be normal. The retinal damage involved in the impairment of dark adaptation in the cases in this series was presumably hypoxic in character but not sufficiently severe to cause a subnormal clinical ERG. The oscillatory potentials in the ERG were studied in two cases in this series and were slightly reduced in both cases. Numerous previous authors observed a reduction of the oscillatory potentials in diabetic retinopathy even in cases in which the lesion was very mild in character (Yonemura et al 1962, Sugita et al 1963, Simonsen 1965, 1966, Kojima et al 1966, Nakajima & Sugimachi 1966). Simonsen (1966) found abnormal oscillatory potentials in diabetics even in the absence of ophthalmoscopic evidence of retinopathy.

Discussion

Nothing definite can be said at this stage about the factors involved in the impairment of dark adaptation in the cases presented in this paper. However the possibility cannot be excluded that hypoxic damage to the retina in conjunction with a disturbance of the vitamin A synthesis was a contributory factor. The changes in the dark adaptation pattern after photocoagulation were negligible despite the fact that a relatively large retinal area was coagulated and from 110 to 130 photocoagulation lesions were produced. Of the nine patients in the age group 20-40 years four patients showed no change in dark adaptation after treatment, two patients showed a slight improvement (the values obtained were within the normal range after 25 minutes in the dark in one of them) and the remaining three patients showed slight impairment of dark adaptation after photocoagulation. Of the 11 patients in the age group 40 to 60 years no change occurred in dark adaptation after treatment in 9 patients, one patient showed slight improvement and one showed slight impairment of dark adaptation.

As already mentioned the changes in the appearances of the curves after

Grade IV : Ectopia combined with anomalies of constitution
Marfan's syndrome Marfan's syndrome Ehlers Danlos
syndrome

Some authors describe simple ectopia lentis as an abortive type of Marfan's syndrome. In recent years homocystinuria has been added to the last group.

Most of the pathological and histological examinations have been carried out on eyes from patients with Marfan's syndrome (Reh & Lehman 1954; Wachtel 1966). These reports are based on an ordinary light microscopic technique. The lenses are reported to be small and spherical and the zonules appear defective with an abnormal attachment to the lens. Lund & Sjötoft (1950) have also reported defective or absent zonular apparatus in an extensive clinical review.

The purpose of this investigation has been to examine the lenticular part of the zonular apparatus in congenital simple lenticular ectopia and make a comparison between the ectopic lens and a normal one in order to shed some light on the existence of deep capsular insertions of the zonule.

Material and Methods

One ectopic and one normal lens were examined with scanning and transmission electron microscopic techniques. The ectopic lens was removed from a 23 year old male patient with congenital simple ectopia lentis. In his family this condition could be traced through three generations (Fig. 1). The patient had bilateral ectopic lenses diagnosed almost from the time of birth. In May 1971 he was admitted to the Eye Department Haukeland Hospital with an acute dislocation of the right lens into the anterior chamber. The dislocated lens was successfully removed with a cryoextractor and after a somewhat

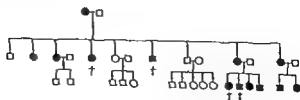


Fig. 1

Diagram showing the occurrence of simple ectopia lentis. ○ female members □ male members. Dark symbols affected individuals. X the patient.

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THE LENTICULAR ATTACHMENT OF THE ZONULAR APPARATUS IN CONGENITAL SIMPLE ECTOPIA LENTIS

BY

JOHAN H SELAND

One normal and one ectopic lens have been examined with scanning and transmission electron microscopy. Some areas of the lens from the abnormal eye were completely devoid of zonular threads while some irregular remnants were present in other areas. The ultrastructure of the capsula propria was essentially identical to the ultrastructure seen in a normal lens. The granular inclusions found in the anterior lens capsule are probably not a part of the zonular apparatus.

Key words: human lens capsule - simple ectopia lentis - zonule

True congenital ectopia of the lens is almost invariably bilateral. Clark (1939) has suggested the following subclassification:

- Grade I Simple ectopia lentis
 Ectopic lenses in a grossly normal eye
- Grade II Ectopia combined with anomalies of ocular dimension
 Axial myopia, microphthalmus
- Grade III Ectopia combined with anomalies of ocular structure
 Persistent pupillary membrane, corectopia, aniridia, polycoria,
 coloboma of the uvea and the lens and megalocornea

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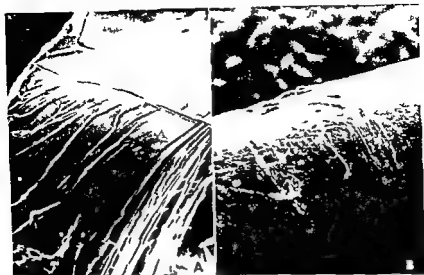


Fig 2

Scanning electron microscopy (SEM) of the anterior equatorial region A Normal lens Thick coiled free zonular threads continuing in radially arranged capsular attachments producing folds that end abruptly near a transverse artifact and continue into smooth capsule B Ectopic lens Irregular arrangement of zonular threads Some areas are devoid of fibres (Original magnifications $\times 100$)



Fig 3

SEM enlargement of Fig 2 A Normal lens Thick free cords with striations segmentations and occasional globular enlargements The capsular fibres are almost parallel B Ectopic lens Small dimensions of the capsular fibres Very few free cords can be seen (Original magnifications $\times 1000$)

prolonged postoperative period he was able to wear contact lenses with full vision (6/6). The left lens was at that time subluxated nasally and upwards. Tests for homocystein and hydroxyproline in the urine were negative. In October 1972 he was readmitted to the hospital because of acute glaucoma due to dislocation of the left lens into the anterior chamber. The lens was removed with a cryoextractor and subjected to electron microscopy. The lens used as a control was removed from a normal eye donated by a 63 year old male for corneal transplantation. Enucleation was done two hours after death and the eyes were kept at 2°C until further processing could take place about ten hours later.

The two lenses were fixed in 4 per cent glutaraldehyde for about 30 min. They were then bisected axially. One half was subjected to scanning electron microscopy and the other half to transmission electron microscopy. The scanning microscopy material was cleaned with ultrasound (Balsonic) for 5 min and fixed in a 50/50 mixture of 4 per cent formaline and 4 per cent glutaraldehyde for 12 h. Most of the nuclear material was removed and the capsule and its cortex were then postfixed in osmium tetroxyd, dehydrated and airdried. They were mounted on stages coated with carbon and gold/palladium and examined in a Jeol JSM U3 scanning electron microscope.

The two halves to be examined in the transmission microscope had most of their nuclear material removed and they were postfixed in osmium tetroxyd, dehydrated and embedded in toto in blocks of Epon. After curing the blocks were reorientated and thin slices were cut with a razor blade in a radial manner. These slices were sub-sectioned into 8 segments, orientated and reembedded individually in Epon, cut with LKB or Reichert ultramicrotomes, stained with uranyl acetate and lead citrate and subjected to microscopy in a Phillips EM 300 apparatus.

Results

Both lenses were clear at the time of removal. The diameter of the normal non fixed lens was 9 mm. The diameter of the non fixed ectopic lens was 7.1 mm. The ectopic lens was more spherical than the normal one.

Examination with scanning electron microscopy (SEM)

In the normal lens scanning electron microscopy of the equatorial region revealed two forms of zonular fibres where one represented the free suspensory ligament and the other its continuation onto the capsular surface. The former was thick and cordlike, lying freely and at random on the capsular surface. This type had an even thickness with occasional globular enlargements. Axial grooves could be observed in the cords and there was also a tendency to cross

scanty in comparison with the normal lens. Some areas were completely devoid of any zonular apparatus while others had a few zonular threads (Fig 2b). Remnants of both forms of zonular fibres could be found. Most of the fibres were small and measured from 1 to 3 μ and very few exceeded 5 μ . However, single aberrant cords with a coagulative appearance have been found and they had a maximal thickness of 20 μ . In some circumscribed areas at the anterior portion of the abnormal zonular insertion, one could see aggregates of small whitish spots (Fig 5 a). Enlargement of such a colony showed structures which did not seem to have any direct connection with the zonular threads (Fig 5 b).

No distinct transition area between the zonular insertion and the anterior capsule could be distinguished. The anterior polar capsule was damaged by the cryoextractor and could therefore not be compared with the normal lens.

The posterior capsule had no characteristic surface structures. It seemed to be identical to the normal capsule.

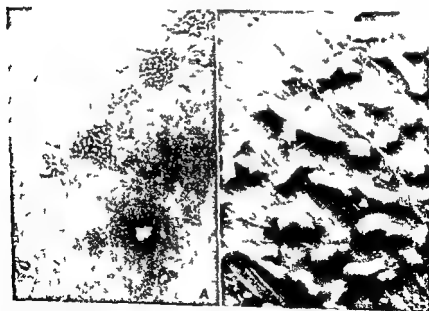


Fig 5

SEM of anterior equatorial region of the ectopic lens. A Three aggregates with whitish spots (Original magnification $\times 100$) B High magnification of one aggregate showing some plump distinctly elongated structures (Original magnification $\times 1000$)

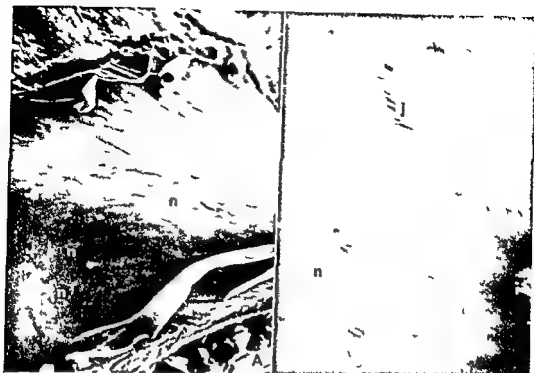


Fig 4

SEM of anterior polar region of the normal lens A Smooth capsule where the nuclei of the epithelial cell (n) strands out in relief (Original magnification $\times 100$) B High magnification of the same region showing a nucleus (n) and a cell junction suture (j) (Original magnification $\times 1000$)

segmentation. This latter phenomenon may, however, be a dehydration artefact. The diameter of the cords varied between 3 and $10\ \mu$ (Figs 2a and 3a).

The other fibre type which represented the proper attachment of the zonular apparatus to the lens was thin and partly fused with the capsule. They were arranged in a radial manner raising the surface to virtually parallel folds on high magnification (Fig 3a). The size of the individual fibre decreased to less than $0.5\ \mu$ as it coursed towards the anterior polar region. 2.2 mm from the anterior pole there was a relatively abrupt transition into a smooth capsule. At the anterior pole the capsular structure seemed smooth and the cell nuclei were seen in relief (Fig 4a). At high magnification the capsular surface has regular shallow radial valley-like depressions. In addition one noticed suture-like serpent structures representing the cell junctions (Fig 4b). The posterior pole of the normal lens was smooth and even and had no characteristic surface relief.

In the ectopic lens the zonular threads in the equatorial region were very

scanty in comparison with the normal lens. Some areas were completely devoid of any zonular apparatus while others had a few zonular threads (Fig 2b). Remnants of both forms of zonular fibres could be found. Most of the fibres were small and measured from 1 to 3 μ and very few exceeded 5 μ . However, single aberrant cords with a coagulative appearance have been found and they had a maximal thickness of 20 μ . In some circumscribed areas at the anterior portion of the abnormal zonular insertion, one could see aggregates of small whitish spots (Fig 5a). Enlargement of such a colony showed structures which did not seem to have any direct connection with the zonular threads (Fig 5b).

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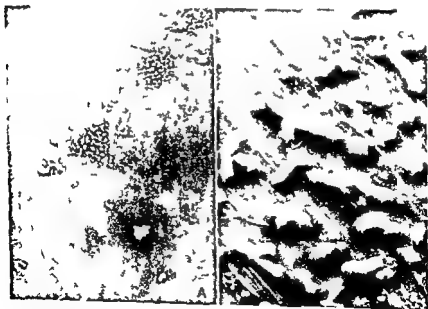


Fig 5

SEM of anterior equatorial region of the ectopic lens. A Three aggregates with whitish spots (Original magnification $\times 100$) B High magnification of one aggregate showing some plump, distinctly elongated structures (Original magnification $\times 1000$)

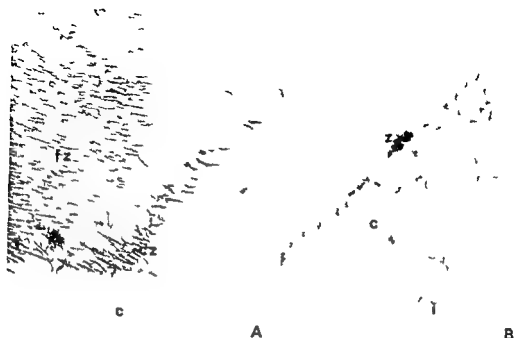


Fig 6

Transmission electron microscopy (TEM) of the anterior equatorial region A Normal lens The lens capsule (c) is lined with capsular zonular fibres (cz) A free zonular thread (fz) is caught in an oblique section B Ectopic lens Only a single zonular fibre (z) is seen in transection on the capsular (c) surface Note the capsular inclusions (i) (Original magnification $\times 30\,000$)

Examination with the transmission electron microscope (TEM)

Most of the features described above were supported by examination with transmission electron microscope. In sections from the anterior equatorial region of the normal capsule the two forms of zonular threads could easily be distinguished. The free zonular cords could be seen as separate entities from the capsule and its surface. Each cord was composed of small fine fibrils with a distinct periodicity measured to about 110 Ångström. The capsular fibres could be seen to line the capsular surface with similar fibrils producing a wavy border and penetrating about $0.1\text{--}0.5\ \mu$ down into the capsular substance (Fig 6a). The sharp transition zone between the capsular fibres and the smooth anterior capsule demonstrated by the scanning pictures could not be found in the transmission sections. Zonular fibres could be traced in all sections of the anterior capsule except from the polar 2 mm.

Under the capsular surface one found the granular inclusions described

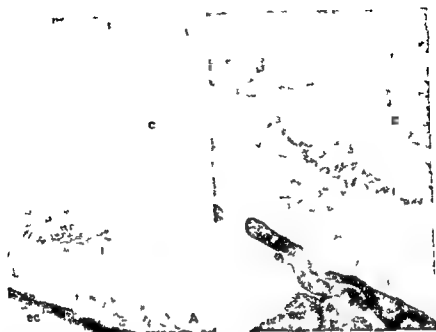


Fig 7

TEM of the anterior equatorial region at the capsuloe epithelial junction A Normal capsule Several inclusions (i) are seen in the capsular substance (c) Near the epithelium (ec) one inclusion exhibit a periodicity of 490 \AA B Ectopic lens Inclusions (i) in the lens capsule (c) near the epithelial cell (ec) (Original magnification $\times 50\,000$)

by Jakus (1964) and Cohen (1965) These inclusions could be seen throughout the whole thickness in the bow areas of the normal capsule (Fig 7 a)

In the anterior equatorial region of the ectopic lens one found areas which were completely devoid of any zonular fibres Neighbouring areas might however show some indication of a wavy border with zonular fibrils No trace of zonular fibrils could be demonstrated near the anterior polar region Irrespective of the presence or absence of surface fibrils the capsule itself contained a large number of granular inclusions throughout the whole capsular thickness in the bow area These inclusions could also be found near the epithelial surface (Figs 6 b and 7 b) In the lenses no inclusions were found towards the posterior pole

When evaluating the different measurements one has to bear in mind that an airdried scanning microscopy specimen has been subjected to a 30 per cent shrinkage from the native state The transmission specimens are similarly subjected to a shrinkage between 10 and 20 per cent

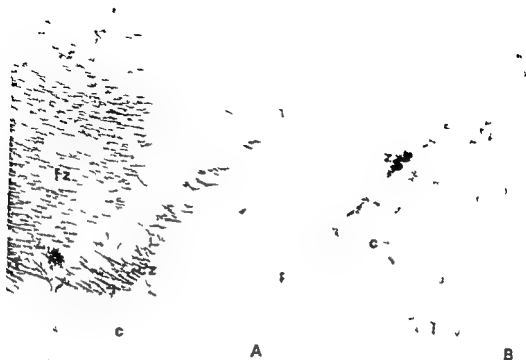


Fig 6

Transmission electron microscopy (TEM) of the anterior equatorial region A Normal lens The lens capsule (c) is lined with capsular zonular fibres (cz) A free zonular thread (fz) is caught in an oblique section B Ectopic lens Only a single zonular fibre (z) is seen in transection on the capsular (c) surface Note the capsular inclusions (i) (Original magnification $\times 30\,000$)

Examination with the transmission electron microscope (TEM)

Most of the features described above were supported by examination with transmission electron microscope. In sections from the anterior equatorial region of the normal capsule the two forms of zonular threads could easily be distinguished. The free zonular cords could be seen as separate entities from the capsule and its surface. Each cord was composed of small fine fibrils with a distinct periodicity measured to about 110 Ångström. The capsular fibres could be seen to line the capsular surface with similar fibrils producing a wavy border and penetrating about 0.1–0.5 μ down into the capsular substance (Fig 6 a). The sharp transition zone between the capsular fibres and the smooth anterior capsule demonstrated by the scanning pictures could not be found in the transmission sections. Zonular fibres could be traced in all sections of the anterior capsule except from the polar 2 mm.

Under the capsular surface one found the granular inclusions described

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THE OPHTHALMOPLEGIC FORM OF THE GUILLAIN BARRE SYNDROME AN IMMUNOLOGIC STUDY

BY

PETER O BEHAN and NORMAN GESCHWIND¹

ABSTRACT

The exact pathogenesis of the ophthalmoplegic form of the Guillain Barre syndrome is not understood. Detailed immunologic studies in a classical case of this entity showed cell mediated immunity to peripheral nerve antigens but not to central myelin antigens. It is concluded that this syndrome is a true variant of Guillain Barre polyneuritis and that the lesions are peripheral and not central as often postulated.

Key words: Guillain Barre's syndrome - ophthalmoplegia - immunology

The Landry Guillain Barre Strohl syndrome (LGBS syndrome) classically presents as an ascending motor paralysis with minimal sensory involvement although subjective paresthesia in the feet and hands is common. The illness usually appears in the wake of a banal viral infection but can occur in a

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Discussion

This investigation has supported earlier light microscopic examinations and showed that ectopic lenses have a grossly deficient and abnormal zonular apparatus. Both the free suspensory zonular cords and the capsular attachment fibres are underdeveloped in the ectopic lens. The congenital ectopia therefore seems to be a result of defective development of the zonular apparatus.

Allowing for the age differences, the proper lens capsule of the two lenses seemed to be almost identical both with regards to the architecture and the presence of capsular inclusions which in the equatorial regions could be traced right down to the lens epithelium. These granular inclusions have been interpreted by some authors as being part of the zonular apparatus and representing its deep insertion (Porte et al 1971, Raviola 1971). However, it seems improbable that a vestigial and abnormal extracapsular zonular apparatus has a completely normal deep intracapsular anchorage. It seems therefore unlikely that the granular inclusions represent a part of the zonular threads.

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Gait was not tested but there was mild incoordination of the upper limbs on finger to nose testing. Cerebellar testing of the lower limbs was prevented by the concomitant weakness.

Laboratory data

Urinalysis showed a trace of protein, 10-20 white cells and mild infection with *E. coli*. Hematocrit was 43, WBCs 12,600 with 83 neutrophils. A Hinton test was negative. BUN, creatinine, blood sugar, electrolytes, cholesterol, prothrombin time, bilirubin, total protein, albumin, SGOT, LDH, alkaline phosphatase and amylase were all within normal limits. Lumbar puncture on admission was normal with a total protein of 33 mg per cent; five days later the protein had risen to 64 mg per cent. Blood and sputum cultures were all negative. A chest X-ray showed a left lower lobe infiltrate which cleared within three days. Tests for cold agglutinins were negative, as were tests for porphyria. Viral studies were unhelpful. An I.E. prep was negative, as were tests for anti-nuclear antibodies and infectious mononucleosis. The patient was further tested for occult carcinoma but chest films and barium meals and enemas were all negative. A muscle biopsy was compatible with denervation atrophy and a sural nerve biopsy was essentially normal.

Hospital course

The patient remained in hospital two full months and was treated with prednisone 20 mg q.i.d. Initially her weakness became more pronounced, as did the cerebellar findings in her arms with complete loss of deep tendon reflexes. Over the remaining time she regained full use of the extraocular muscles. The reaction of the pupils to light remained sluggish and there was no pupillary response to attempted accommodation. Her peripheral muscle weakness improved and steroid treatment was tapered off. She was seen three months later and had made a full recovery.

Immunologic Studies

Serum proteins

The total serum protein was 5.9 g with IgG 430 mg% (normal 600-1500), IgA 700 mg% (normal 30-200 mg%) and IgM 89 mg% (normal 50-200). Tests for cryoglobulin and euglobulin were negative. Total haptoglobin was 450 mg% and alpha 1 anti-trypsin 160 g N (N 65%-135%).

These changes were consistent with an acute inflammatory process. The mild reduction in IgG most probably reflected the fact that the patient was on steroids at the time of the determination.

Cell mediated hypersensitivity

Lymphoblast transformation was performed twice with the use of short term cultures of lymphocytes obtained from the patient's peripheral blood. In brief, the method con-

variety of other circumstances e.g. after immunizations during fever therapy after operations and in association with malignant disorders (Behan & Behan 1970). The mode of presentation, the parts of the nervous system involved and the clinical course show great variability. One rare mode of presentation of this disease is that which primarily affects the oculomotor nerves (Elizán et al 1971). An even rarer presentation is that of complete ophthalmoplegia with an associated internal ophthalmoplegia. Controversy exists as to the exact site of the lesion causing the ophthalmoplegia since pathological studies have been performed in only a few fatal cases. We were fortunate in being able to study clinically and immunologically an 85 year old woman with this variant of Guillain Barre disease.

Case History

An 85 year old Negro woman entered Boston City Hospital on 17/7/69 complaining of generalized weakness and an inability to move her eyes. She had been in reasonable health up until three weeks previously when she developed an influenza like illness with fever, sore throat, cough and generalized aches. Two weeks later she noticed that she was becoming weak and had difficulty reading. Within a day or so she could not move her eyes and her relatives noted she was walking unsteadily. She had a long history of bronchial asthma and suffered from congestive heart failure which was controlled on digitalis and diuretics. Ten years previously she had had an adenocarcinoma of the colon removed.

On admission the general physical examination was unremarkable except for poor respiratory movements with coarse scattered rales heard over both lung fields. Blood pressure was 180/90, pulse 80 and regular, T 99°F. Neurological examination showed her to have a clear mental status; she was able to give a good account of her illness and the events of the day. Visual fields were normal to confrontation and on perimetry. Visual acuity was 20/30 in each eye with glasses and the fundi were normal except for a small flame shaped hemorrhage over the right disc. There was total external ophthalmoplegia with the eyes in the primary position. The patient was unable to move her eyes either on command or on doll's head maneuver. Bell's phenomenon was absent and infusion of 30 ml of cold water in either ear failed to move her eyes. There was no nystagmus and the optokinetic response was also absent. The pupils were dilated OD 5.5 mm and OS 6.5 mm with no response to light in the left eye and a minimal sluggish response in the right. There was no pupillary response to attempted accommodation. Corneal sensation was intact. There was bilateral ptosis greater on the left side. The remaining cranial nerves were normal except for mild weakness of the orbicularis oculi muscles bilaterally.

She could move all her limbs but had generalized weakness more conspicuous in the lower limbs at the hip flexors. Deep tendon reflexes could only just be obtained in the arms and could not be elicited in the legs. The plantar response was flexor bilaterally.

nized. Possibly the exact diagnosis is not reached in all cases and there are very few pathological reports of this condition. Controversy exists as to its precise nature and etiology and as to the exact site of the lesion. Some authors claim there is central nervous system involvement while others maintain that only peripheral nerves are involved. We were fortunate in having a case of this variant of LGBS to study and we were able to utilize modern immunological methods to investigate its etiology and the possible site of these lesions.

Lymphocyte transformation is the morphological enlargement and proliferation of small lymphocytes to larger lymphoblasts and this change is accompanied by an increase in the cell DNA. Such change occurs in sensitive lymphocytes on contact with the sensitizing antigen, is specific for that antigen alone and is indicative of delayed hypersensitivity (Valentine 1961). This principle is the basis for the *in vitro* test of lymphocyte transformation in which peripheral blood lymphocytes are grown in short term cultures with a variety of antigens to which the patient is known or suspected to be sensitive. In our patient this test demonstrated good correlation of delayed hypersensitivity to streptokinase/streptodornase antigen as measured *in vivo* (skin tests) and *in vitro* by lymphocyte transformation. A stimulation index of twice control is considered signifi-

Table 1

Antigen	Results Average counts per minute (cpm) per three cultures	Average counts with antigen
		Average counts without antigen (control) (stimulation index)
None	656	1.00
Human BP	896	1.23
Monkey BI	714	1.09
Guinea pig BP	701	1.0
Human peripheral nerve in saline	2313	3.85
Acid extract human peripheral nerve	2906	4.43
Streptokinase/streptodornase	2704	3.9

sisted of withdrawing 80 ml of venous blood into a heparinized syringe and allowing the red cells to sediment. The leukocyte rich supernatant was then centrifuged at 1000g for 10 min. The cell pellet was washed three times in phosphate buffered saline and transferred to tissue culture fluid made up of T.C. 199 with antibiotics and 10% autologous serum. Culture tubes were set up in triplicate each containing 1×10^6 lymphocytes in one ml of tissue culture fluid. The antigens used were the following: 1) Human monkey and guinea pig encephalitogenic myelin basic proteins at a concentration of 25 $\mu\text{g/ml}$; 2) 0.1 ml of finely homogenized human sciatic nerve in saline containing 0.0025 mg dry nerve matter. This was heated to 56°C for one hour prior to use; 3) A crude acid extract of human sciatic nerve. This was prepared by treating successively cleaned human sciatic nerve with chloroform/methanol (2:1 V/V) and acetone and water for 24 hours. The residue was further extracted with dilute hydrochloric acid at pH 3.0. This material was used at a concentration of 25 $\mu\text{g/ml}$; 4) Control antigens consisted of streptokinase streptodornase at a concentration of 50 units per culture tube; 5) Cultures without antigen acted as negative controls.

The cultures were incubated in tightly stoppered glass vials at 37°C for six days. Twenty-four hours prior to harvest 2.5 μCi ^3H thymidine (sp. activity 61 Ci/mmol) (New England Nuclear) were added to each culture. The cells were then removed, washed 4 times in saline and frozen and thawed twice. The pellet was resuspended in saline and the DNA precipitated by 10% cold trichloroacetic acid. The precipitate was allowed to dry by inverting the tubes for 4 hours. The precipitate was dissolved in 0.5 ml NCS reagent (Nuclear Chicago) and resuspended in 10 ml Bray's Solution. Three 10 minute counts were made on each culture in a scintillation counter (Nuclear Chicago Unicam). The controls without antigen were treated in exactly the same manner. The results were expressed as a number signifying the following ratio:

$$\frac{\text{counts per minute with antigen}}{\text{counts per minute without antigen}}$$

Discussion

There is little difficulty in diagnosis when the clinician is confronted with a patient with classical LGBS syndrome. The history of antecedent illness together with the evolution of clinical signs and the CSI findings make the diagnosis easy. However, this may not be the case when one is presented with one of the clinical variants of this syndrome. In particular that form which affects mainly the oculomotor nerves may suggest at first other diseases such as Wernicke's encephalopathy, vascular disease, tumor of the brainstem or botulism. This variant of LGBS which presents as a bilateral ophthalmoplegia with or without any combination of other cranial nerve palsies and with or without generalized systemic motor nerve involvement is not well understood. Indeed this variant has received little attention in the English literature although it was first described in 1932 (Collier 1932). More and more cases are now being recog-

ized. Possibly the exact diagnosis is not reached in all cases and there are very few pathological reports of this condition. Controversy exists as to its precise nature and etiology and as to the exact site of the lesion. Some authors claim there is central nervous system involvement while others maintain that only peripheral nerves are involved. We were fortunate in having a case of this variant of LGBS to study and we were able to utilize modern immunological methods to investigate its etiology and the possible site of these lesions.

Lymphocyte transformation is the morphological enlargement and proliferation of small lymphocytes to larger lymphoblasts and this change is accompanied by an increase in the cell DNA. Such change occurs in sensitive lymphocytes on contact with the sensitizing antigen is specific for that antigen alone and is indicative of delayed hypersensitivity (Valentine 1971). This principle is the basis for the *in vitro* test of lymphocyte transformation in which peripheral blood lymphocytes are grown in short term cultures with a variety of antigens to which the patient is known or suspected to be sensitive. In our patient this test demonstrated good correlation of delayed hypersensitivity to streptokinase/streptodornase antigen as measured *in vivo* (skin tests) and *in vitro* by lymphocyte transformation. A stimulation index of twice control is considered signifi-

Table I

Antigen	Results Average counts per minute (cpm) per three cultures	Average counts with antigen
		Average counts without antigen (control) (stimulation index)
None	636	1.00
Human BP	896	1.23
Monkey BP	714	1.09
Guinea pig BP	61	1.0
Human peripheral nerve in saline	2343	3.83
Acid extract human peripheral nerve	2906	4.43
Streptokinase/streptodornase	7601	3.91

Table II

Clinical data in cases of the ophthalmologic form of LCBS

Principal author	Age/ex	Ophthalmologic signs	Protrusion	Pupil	Bell's	Doll's	OKN	Calories
Van Bogaert et al 1938	6 M	+		Abn	NM	NM	NM	NM
Maisson Verniory 1940	34 F	+	+	Abn	NM	NM	NM	NM
	41 M	+	+	Abn	NM	NM	NM	NM
	32 F	+	+	Abn	NM	NM	NM	
Haymaker & Kernohan 1949		+						
Bickerstaff & Cloake 1951	24 F	+	+	Norm	NM	NM	NM	
	36 M	+	+	Abn	NM	NM	NM	
	24 F	+	+	Abn	NM	NM	NM	
Fisher 1956	45 M	+	+	Abn	Abn	Abn	NM	
	65 M	+	-	Abn	Abn	NM	NM	
	63 M	+	+	Abn	Press	Norm	NM	
	49 F	+	+	Norm	Pres	NM	NM	No effect
	24 F	+	+	Norm	NM	NM	NM	NM
Smith & Walsh 1957	38 M	+	+	Norm	NM	NM	NM	No effect
	63 M	+	+	Abn	NM	NM	NM	NM
Neubert 1958	19 F	+	-	Abn	NM	NM	NM	NM
Darcourt & Lossa 1959	66 F	+	+	Norm	NM	NM	NM	NM
Arnould et al 1960	36 F	+	-	Abn	NM	NM	NM	NM
Hynes 1961	40 F	+	+	Abn	NM	NM	NM	NM
Ashworth 1963	61 F	+	+		NM	NM	NM	NM
	65 M	+		Abn	NM	NM	NM	NM
Bignami & Servi 1965	35 M	+						

Ophthalmoplegic Form of Guillain Barre's Syndrome

Cranial nerves	Ataxia	Motor weakness	Reflexes	Objective sensory signs	CSF proteins mg ^o /o	Duration & outcome
7		+	Absent	Normal	960	Rec in 2 h
9 10	-	-	Decr	Normal	100-200	Rec in 7 mos
7 9 10	+	+	Absent			Diplopia after 3 months
3 7	+	+	Absent	Normal	1000	Rec 2 months
7 9 10						
3 5 7 9 10	+			L Facial Sensory loss	40-77	Rec 9 months Incomplete rec 4 mos
5 7 9 10	+			Deaf		Rec 4-6 months
5 (9 10?)	+	+	Absent	Vibration impaired	36-343	Impr 6 weeks
None	+	-	Absent	Norm		Impr 5 weeks
None		-	Absent	Norm	30	Mod rec after 3 months
9 10		+	Absent	Numbness L hand	14-54	Impr 3 months
		+				Died after 43 days
	-	+	Decr	Facial numbness	45-50 70-40	Rec 60 days
9 10	-	+	Absent	Normal	50-97	No impr 5 weeks
7 9 10		+	Absent	Position sense	900	Recovered
none			Absent	deficit	2300-5000	Diplopia after 5 months
none		-	Absent	Normal	50-75	Eyes affected after 1 year
9 10 11		+	Absent	Sense loss in digitalis vibration	159	Impr 5 mo
9 10	+	+	Absent			
	+	+	Absent	Touch & norm pinprick		Rec 3 mo Rec 6 mo
9 10 11						
					increas	Died day 1 ^o Histology positive

Table II (cont)

Principal author	Age/sex	Ophthalmoplegia	Ptosis	Pupil	Bells	Dolls	OAN	Caloric
Goodwin & Poser 1963	54 M	+	+	Abn	NM	NM	NM	NM
Kelly & Gibberd 1963		+		Abn	NM	NM	NM	
		+		Abn	NM	NM		
Van Allen & MacQueen 1964	1 F	+	+	Abn	NM	NM	No effect	
same patient	61 M	+	+	Norm	NM	NM	Abs	
	6 F	+	+	Abn				
	11 F	+	+	Abn	Abs	Abn	Abs	
	36 M	+	+	Norm	NM	NM	NM	
Munsat & Barnes 1965	5 M	+	+	Norm	NM	NM	NM	
	20 M	+		Norm	NM	NM		
	40 F	+						
	24 M	+		Norm	NM	NM	NM	
Lord 1966	17 M	+		Norm	NM	NM	NM	
Patel et al 1966	80 M	+	+	Norm	NM	NM	NM	
	6 F	+		Norm	NM	NM	NM	
Asbury et al 1969	64 M	+						
	31 F	+						
	24 F	+						
Bell et al 1970	5 M	+	+	Abn				
same patient	6 F	+	+	Abn	Abs	Abs	Abs	
	12 F	+	+	Abn	Abs	Abs	Abs	
	1 F	+	+	Abn				
Adams 1971	49 M	+	+	Abn	Abs	Abn		

Ophthalmoplegic Form of Guillain Barre's Syndrome

Cranial nerves	Ataxia	Motor weakness	Reflexes	Objective entory signs	CSF proteins mg ^o /	Duration & outcome
9 10 11 1 ^o 9 10	+	+	Absent		24-53	Weakness after 6 weeks
		+	Absent	Normal	Norm - +60-80	
		+	Absent	Normal	Norm - +60-80	
7			Absent	Reduced peripheral sense	31	Clinical signs cleared rapidly
	+		Decreased		71	
		+	Decreased		150	Rapid recovery
	+	+	Absent	Normal	130	
	+		Absent		210	
		-	Absent	Normal		Rec 7 day
	+	-	Norm	Normal	50	Rec 5 mo
9 10	-		Decreased	Normal	Normal	Rec rapid & progressive improved 3 mo
9 10	-			Pin & touch decreased in feet		
9 10		+	Absent	Normal	Norm 2, 3	Rec 4-6 mo
		+	Absent	Vibration poor	109	Rec 6 mo
		+	Absent	Normal	23-53	Rec 2 mo
9 10		+	Absent		76	Died day 4
9 10 11		+	Absent	Touch decreased	40-144	Died day 3
9 10 1		+	Absent	in limbs	40	Died day 44
		+	Decr	Norm	9 3	Improved 1 year
		+			133	Rec 1 mo
		+	Absent	Norm	133-150	Rec 2 years (decr reflexes)
none		-	Decr Absent	Norm Norm	31 33-50-71-94 133-171-94	Rec 3 years Improved 1 ^o weeks

Table II (cont)

Principal author	Age/sex	Ophthalmoplegia	Ptosis	Pupil	Bell's	Doll's	OKN	Caloric
Elizan et al 1971	27 M	+	+	Norm				
	6½ M	+	-	Abn				
	49 M	+	+	Norm				No effect
	19 M	+	+					
	39 M	+	+	Abn				
	54 M	+	-	Norm				
	57 F	+	+	Abn	Abn	Abn		No effect
	30 M	+	+	Norm				
	60 F	+	-	Abn				
	22 M	+	-	Norm	Press			Poor effect
Jampel & Haidt 1972	56 F	+	-	Abn				
	24 F	+	+	Abn	Press	Abn		

** NM = Not Mentioned REC = Recovered

cant The patient therefore demonstrated cell mediated hypersensitivity to peripheral nerve and peripheral nerve myelin proteins This sensitivity to myelin antigens has been previously demonstrated in patients with classical LGBS by means of a similar *in vitro* technique of lymphoblastic transformation (Behan et al 1969 Caspary et al 1970) and another *in vitro* method i.e macrophage inhibition (Rocklin et al 1971 Behan et al 1972) There was no sensitivity to central myelin antigens It is known that sensitivity to central myelin antigens may occur when central nervous system (CNS) tissue is involved in allergic reactions (Behan et al 1965) This test therefore confirms that this patient's illness was a variant of LCBS and that there was no immunological involvement of the CNS

Ophthalmoplegic Form of Guillain Barre's Syndrome

Cranial nerves	Ataxia	Motor weakness	Reflexes	Objective sensory signs	CSF proteins mg%	Duration & outcome
none	+	+	Decr	Norm	43-138	Rec 3 mos
none	-	+	Decr	Decr vibration	31	Weakness 9 weeks
9 10	+	+	Absent	Decr vibration	300-500	Rec 9 weeks (nystagmus)
7	+	-		Normal	94	Diplopia 4 mo
none	+	-	Absent	Normal	30	Impr 6 weeks
none	+	-	Absent	Normal	59-85	No change 3 weeks
none	+	-	Absent	Numbness decr touch	100-147	Diplopia 11 mos
none		-	Absent	Normal vibration	44-61	Rec 7 mos
none		-	Absent	abs in limbs	40-52	Rec 39 days
9 10 12	+	+	Decr	Decr vibration pinprick stereognosis	37-54 67-95	Improved 18 days
9 10		+	Absent			Rec 4 1/2 weeks
9			Absent	Decr pain sense	94-43	Rec 4 mos
10 11 1	-					

NM Not Mentioned REC Recovered

An analysis of the clinical data of our patient and of those cases reported in the literature further support these findings. Complete ophthalmoplegia with internal ophthalmoplegia is rare (Table II). The oculomotor nerves can be either partially or completely involved with or without sparing of the pupil. In our case there was no reaction to Bell's phenomenon, accommodation, doll's head maneuver, caloric stimulation, or optokinetic nystagmus. The sparing of Bell's phenomenon in the face of complete ophthalmoplegia occurs very rarely (Jampel & Haidt 1972) and only two other cases have been recorded (Fisher 1971). This preservation of Bell's phenomenon has been offered as evidence that there is a supranuclear component in this form of LGBS (Jampel & Haidt 1972). Indeed, several authors suggest that there may be such central involve-

Table II (cont)

Principal author	Age/sex	Ophthalmoplegia	Ptosis	Pupil	Bell's	Doll's	OKN	Calories
Elizan et al 1971	27 M	+	+	Norm				
	68 M	+	-	Abn				
	49 M	+	+	Norm				No effect
	19 M	+	+					
	39 M	+	+	Abn				
	54 M	+	-	Norm				
	57 F	+	+	Abn	Abs	Abn		No effect
	30 M	+	+	Norm				
	60 F	+	-	Abn				
	22 M	+	-	Norm	Press			Poor effect
Jampel & Haidt 1972	56 F	+	-	Abn				
	24 F	+	+	Abn	Press	Abn		

** NM = Not Mentioned REC = Recovered

cant The patient therefore demonstrated cell mediated hypersensitivity to peripheral nerve and peripheral nerve myelin proteins This sensitivity to myelin antigens has been previously demonstrated in patients with classical LGBS by means of a similar *in vitro* technique of lymphoblastic transformation (Behan et al 1969 Caspary et al 1970) and another *in vitro* method i.e macrophage inhibition (Rocklin et al 1971 Behan et al 1972) There was no sensitivity to central myelin antigens It is known that sensitivity to central myelin antigens may occur when central nervous system (CNS) tissue is involved in allergic reactions (Behan et al 1968) This test therefore confirms that this patient's illness was a variant of LGBS and that there was no immunological involvement of the CNS

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ment The remarkable symmetry of the external ophthalmoplegia the recovery of conjugate lateral gaze which was always symmetrical the sparing of the levator palpebral (in some cases) and the pupillary reaction to light suggested to Fisher (1956) "a more centrally placed interruption" He points out further that "the perfect alignment of the eyes during the period of complete immobility has usually been interpreted as indicative of a supranuclear lesion" The tendency to preserve downward gaze might also be considered as a point in favor of central involvement

The unequal bilateral ptosis in our case and the nature of the other cranial nerves involved i.e. bilateral facial nerve palsy together with the systemic motor neuropathy suggest peripheral nerve lesions As can be seen from Table II the recorded cases show that the cranial nerves involved have peripheral lesions and that simultaneous symmetrical recovery is not often found There is little known of the pathology in this variant but in those cases studied at post mortem lesions were found in the cranial nerves (Bignami & Servi 1968 Asbury et al 1969) These lesions are identical to those found in LGBS The third nerve neurons may occasionally show some changes but these are secondary to axonal involvement

Ataxia has been well described in cases of LGBS syndrome It often occurs in association with the variant described here as seen from Table II In post mortem investigations lesions have never been found in the cerebellum or its connections but lesions to explain such cerebellar findings have been found in the spinal cord Demyelination occurs in the posterior roots with secondary fiber loss in the posterior and spinocerebellar columns (Richter 1962) Clarke's column may show complete loss of myelin fibers explaining the ataxia which is secondary to peripheral nerve demyelination This cause of ataxia has not often been demonstrated A long duration of time 46-77 days is necessary for this degeneration to occur and fatalities in LGBS usually occur if at all within the first month from onset of symptoms

Our case therefore tends to support the theory that this illness is a variant of LGBS in which there is delayed hypersensitivity to peripheral nerve myelin and that the lesions occur peripherally without primary central nervous system involvement

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RETINOBLASTOMA IN SWEDEN

A study of 45 children with retinoblastoma
with special regard to the therapeutical results

BY

T JERNDAL E LINDSTEDT T SVENSSON and G ÅKERSKOG

Forty five cases of retinoblastoma in Sweden treated from 1909-1965 are reviewed. A variety of conservative methods were used in 93 eyes of which 13 were cured by radiotherapy. Local application of ^{60}Co was found to be the most favourable method.

Key words: retinoblastoma - radiotherapy - ^{60}Co

While reviewing a material of Swedish children with severe visual impairment (Lindstedt 1970) we found that the fate of the individuals treated for retinoblastoma showed variations to a remarkable degree. The aim of this study is to evaluate the various therapeutic measures used and if possible to advocate a therapy of choice.

Methods of collecting the material

The Swedish Cancer Register was founded in 1959 and from this source 37 cases were traced in the period 1959-1965. The reporting institution usually an eye clinic was also registered and was contacted for the medical record of each case.

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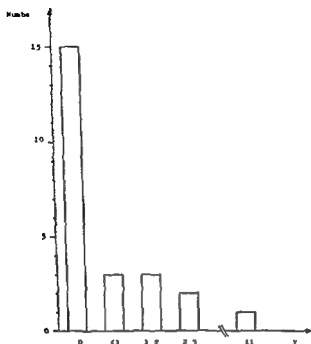


Fig 9

Bilateral retinoblastoma (74 cases) Interval between affection of both eyes

first examination In the remaining 9 cases with eventual bilaterality the time interval between discovery of the tumour in the two eyes is given graphically in Fig 2

The symptom which brought the child to examination was usually leukokoria the white greyish appearance of the pupil Other symptoms are given in Table 1

Therapeutic measures

The present material of 45 cases of retinoblastoma (69 eyes) has been treated with one or a combination of the following therapeutic measures

I Radical method

- a Enucleation of the bulb

II Conservative methods

- a Radiotherapy with conventional X ray radiation
- b Radiotherapy with high voltage X ray
- c Radiotherapy with local application of ^{60}Co on the episclera

Another 8 cases all with bilateral retinoblastoma were collected from the Board for blind children

In all 45 cases treated in 20 different ophthalmologic or radiotherapeutic clinics will be reviewed

Material

The material consists of 45 children 30 boys and 15 girls 24 cases were bilateral and 21 unilateral It is to be noted that there is a slight overrepresentation of the bilateral cases due to the method of collecting the material Dominant heredity could be established in 3 bilateral and in 1 unilateral case

Onset and course of the disease

The initial symptoms of the tumour were evident within the first year of life in 20 cases another 22 cases were discovered before three years of age and 3 cases after this age (Fig 1) In 15 cases bilateral tumours were found on the

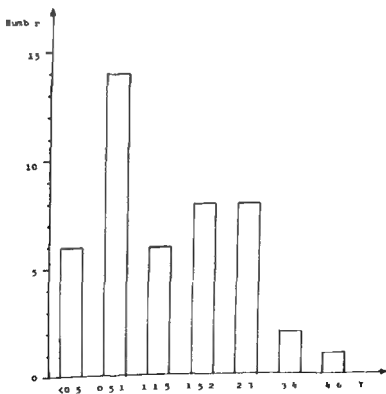


Fig 1
Retinoblastoma (45 cases) Age at affection of first eye

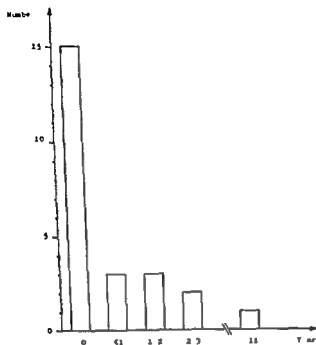


Fig 2

Bilateral retinoblastoma (24 cases) Interval between affection of both eyes

first examination In the remaining 9 cases with eventual bilaterality the time interval between discovery of the tumour in the two eyes is given graphically in Fig 2

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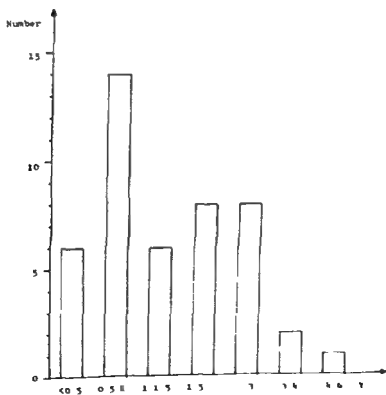


Fig 1
Retinoblastoma (45 cases) Age at affection of first eye

The therapeutic results are given in Tables II-IV

Comment to Table II

6 eyes were removed as the primary treatment and as many as 6 of these were merely group III. The only lethal case was a unilateral tumour of group V and the cause of death was cerebral metastases.

23 eyes were initially given conservative treatment of various kinds. 12 of these 23 eyes were cured and 11 were enucleated because of 1) continued growth of the tumour, of 2) phthisis with no possibility of examining the fundus. Two phthisic eyes were removed, one of which was examined pathologically without sign of vital tumour.

Table II
Primary therapeutic method Number of eyes

Conservative treatment							Enucleation					
Classification Reese	I	II	III	IV	V	total	I	II	III	IV	V	total
Number of eyes	1	9	13	6	1	23			6	4	36	46
Later enucleated		2	7	2		11						
Death											1	

Comment to Table III

23 eyes were given conservative treatment and 13 of these were cured. Every cured eye had been given radiotherapy: 10 eyes by locally applied ^{60}Co and 3 eyes by external radiation.

Both eyes of one child had been given secondary ^{60}Co application by Stallard personally. The eyes were both cured but one eye became phthisic. The cure ratio for external radiation (ortho- and high voltage) is 3/11 and for local application of ^{60}Co 10/12. There is no difference in tumour spread to account for the better results by ^{60}Co .

Comment to Table IV

The average observation time for the ^{60}Co treated cases is 7 years. The unfavourable result of one eye in group III treated with ^{60}Co - it was finally enucleated - deserves further mention. It was treated eight times with local applications and developed cataract. After repeated discussion the eye grew

Table 1

Retinoblastoma 37 cases Symptom which brought the child to examination

White greyish pupil	10
Squint	8
Squint + white pupil	2
Anisocoria	4
Protrusion of the bulb	3
Other specified symptom	4
	57

d Scleral diathermy

e Cytostatic medication with cyclophosphamide perorally or injected as complement to other procedure

f Cytostatic medication (triethylenmelamin) injected intravitreally

g Photocoagulation

In order to evaluate the therapeutic results it is necessary to classify the size and the site of the tumour. We have utilized Reese's internationally recognized classification (Reese 1963) which defines 5 groups

Group I very favourable

a solitary tumour less than 4 dd (disc diameters) in size at or behind the equator

b multiple tumours none over 4 dd in size all at or behind the equator

Group II favourable

a solitary tumour 4-10 dd in size at or behind the equator

b multiple tumours 4-10 dd in size behind the equator

Group III doubtful

a any lesion anterior to the equator

b solitary tumours larger than 10 dd behind the equator

Group IV unfavourable

a multiple tumours some larger than 10 dd

b any lesion extending anteriorly to the ora serrata

Group V very unfavourable

a massive tumours involving over half the retina

b vitreous seeding

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The average observation time for the ^{60}Co treated cases is 1 year. The unfavourable result of one eye in group III treated with ^{60}Co - it was finally enucleated - deserves further mention. It was treated eight times with local applications and developed cataract. After repeated discussion the eye grew

Table III

Methods of conservative therapy Number of eyes Numerals within brackets () designate cure

Classification Reese	I	II	III	IV	V	total
Primary ^{60}Co application			4 (4)	1 (1)	1 (1)	6 (6)
Secondary ^{60}Co application	1 (1)*	1*	2 (1)	2 (2)		6 (4)
External radiotherapy (ortho or high voltage X ray)			2 (1)			2 (1)
External radiotherapy combined with photocoagulation and/or cytostatics		1 (1)	6 (1)	2		9 (2)
						23 (13)

*) Stallard's applicator

Table IV

Therapeutical visual results Number of eyes

Classification Reese	I	II	III	IV	V	total
V > 5/10			4 (2)	1 (1)		5 (3)
2/10-4/10		1	1 (1)			2 (1)
< 2/10-P	1 (1)		1	2	1 (1)	5 (1)
0 (eye removed)		2 ^{b)}	1 (1) ^{b)}	2		11 (1)
						23 (5)

b) One eye phthisic

() Numeral in brackets designates ^{60}Co treatment only

phthisic and was enucleated. No vital tumour tissue could be found on pathological examination.

The eye in group I had a vision of 3/50 after an observation time of 8 years. The poor result is explained by the course of the disease. First was external ortho X ray given in combination with TEM. A recurrence was photocoagulated without success and finally the eye was treated by ^{60}Co with Stallard's disc applicator and this latter treatment cured the eye.

Discussion

The present material of 69 eyes (45 children) with retinoblastoma is collected from 20 Swedish eye clinics – smaller ones as well as university clinics. This explains the great dissimilarity of therapeutic approaches and follow up routines.

Early diagnosis is of paramount importance for a successful therapy in retinoblastoma. Only 3 eyes (3 cases) in this material were diagnosed early enough to be classified in group I and II, one of them a hereditary case.

Nineteen eyes were classified in group III on discovery. Since 3 eyes in group IV were cured with useful vision after radiotherapy, it appears possible to cure and maintain vision in most cases in group I–III.

Thus it is most discouraging to find in our material that 6 eyes in group III were primarily enucleated. Furthermore 2 eyes in group II and 1 eye in group III were finally lost after failure of conservative treatment and 9 patients were bilaterally enucleated.

We therefore conclude that the gain with an early diagnosis can be real only if an efficient method to treat the tumour is available. Judging from this material, radiotherapy is the only efficient method.

Stallard's reports on local application of Radon and ^{60}Co (Stallard 1963 and 1964) have given strong evidence that this method is the therapy of choice for retinoblastoma.

In our material 12 eyes have been treated with a modified ball shaped applicator (Tengroth 1963, Rosengren & Tengroth 1963) and the average tumour dose calculated to 12 000 rad at 1 mm distance from the ball.

The satisfactory cure rate of these 12 eyes (10/12) is comparable to the results of Stallard (1963) and Ellsworth (1965) and we find the visual results very much encouraging in the ^{60}Co treated cases.

The marked discrepancy in our material in favour of ^{60}Co had made it clear that other conservative therapeutic methods have lost their place as the primary

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V > 5/10			4 (2)	1 (1)		5 (3)
2/10-4/10		1	1 (1)			2 (1)
< 2/10-P	1 (1)		1	2	1 (1)	5 (1)
II (eye removed)		2 [§]	1 (1) [§]	2		11 (1)
						23 (6)

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procedure Not only did primary ^{60}Co treatment cure 6 out of 6 eyes but secondary ^{60}Co treatment cured another 4 out of 6 eyes with recurrences after external radiation photocoagulation scleral diathermy and cytostatics

According to the results it appears that the tumour may be selectively destroyed by ^{60}Co radiation and the retina is spared Only 3 cases of certain or radiation cataract are recorded after ^{60}Co and one case was a group V

Another conclusion is that post therapeutic control was not efficiently performed in many cases Check up in general anaesthesia every second month till the age of three years was performed in only one of the clinics Failure in this respect has undoubtedly affected the result

As a consequence of the favourable results with ^{60}Co it is suggested that treatment of retinoblastoma in Sweden be concentrated in one eye clinic specialized in radiotherapeutic facilities including local application of ^{60}Co In that way experience and knowledge in this special field will accumulate and further improvements of the therapeutical procedures can be possible Since the incidence of retinoblastoma in Sweden is approximately six new cases every year one centre would be sufficient for this country and may even give service to other Scandinavian countries

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THE NORMAL ELECTRO OCULOGRAM (E O G)

BY

ALISTAIR ADAMS

Electro oculography was performed on 100 normal subjects (240 eyes) between 10 and 69 years of age with an even sex and age distribution. F O G ratio showed a significant sex difference ($P < 0.01$) with females having higher E O G ratios than males.

There was a significant negative linear correlation between E O G ratio and age in females ($P < 0.01$) but none in males.

Close correlation in E O G ratio was found between right and left eyes ($P < 0.01$) and 95% of subjects showed a difference of 80 or less between right and left eyes.

New normal limits of E O G ratio are proposed. These are 150 to 290 for all males and for females of 50 or more years of age and 140 to 340 for females below the age of 50 years.

A y u d electro oculogram - E O G - ocular standing potential - normal variation

Since Arden et al (1969) described the electro oculogram (E O G) in its present clinical form it has been widely used as an objective test of retinal function.

It is known that F O G ratio shows a wide variation among normal subjects so that to interpret clinical E O G results the limits of this normal variation should be known. Since most diseases which affect the E O G ratio reduce it the lower limit of normality is the most important one. This has

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The Normal E O G

Table I
E O G ratios (per cent) of 170 normal subjects (940 eyes)

		Male											
Age (years)		10-19		20-29		30-39		40-49		50-59		60-69	
Side		R	L	R	L	R	L	R	L	R	L	R	L
E.O.G. ratio		991	187	900	189	177	178	185	185	189	200	167	213
		237	950	200	212	172	214	278	230	250	187	233	273
		171	173	188	188	189	169	910	209	192	193	220	290
		272	237	180	199	177	153	210	914	233	914	183	154
		911	990	960	233	973	215	180	190	921	233	167	164
		300	972	242	297	344	233	188	175	218	300	187	267
		933	933	954	921	300	243	200	223	182	167	214	187
		940	903	170	164	200	199	212	203	200	180	175	178
		914	915	189	220	176	177	907	200	256	933	200	900
		933	178	900	190	181	220	260	300	275	299	200	190
Mean		998.75		905.60		908.90		215.75		214.40		202.35	
Mean (males)		912.65											
Mean (all)		293.84											
Mean (females)		233.84											
Mean		235.95		943.95		249.05		947.85		905.15		218.50	
F.O.G. ratio		900	187	250	235	300	230	210	910	193	192	214	200
		977	955	909	970	960	246	967	943	183	189	233	164
		300	360	977	992	222	977	955	940	936	183	950	223
		173	178	933	269	973	900	300	292	192	227	260	255
		7	955	943	275	337	316	977	900	173	169	167	200
		353	977	194	917	193	906	940	255	231	183	190	200
		40	255	991	969	955	930	917	900	957	900	236	237
		90	913	971	217	175	180	945	261	150	907	237	200
		95	183	990	973	960	40	950	960	275	250	255	931
		18	16	977	906	300	956	319	921	917	186	212	189
Side		R	L	R	L	R	L	R	L	R	L	R	L
Age (years)		10-19		20-29		30-39		40-49		50-59		60-69	
		Female											

been assessed as 150 % (Hirata 1969) 165 % (van Lith & Balik 1970) 185 % (Arden & Barrada 1962) and 200 % (Krill 1966). These studies showed considerable variation both in the number of subjects tested and in their age and sex distribution. It seemed that some of the differences between their results might be resolved by a study of the F O G ratios in a large group of normal subjects with an even distribution of sex and age.

Material

The subjects were 120 normal volunteers. There were 10 males (20 eyes) and 10 females (20 eyes) in each of the six decades between 10 and 69 years. All subjects were in good general health, had neither personal nor family history of ocular or systemic disorders, and had a corrected visual acuity of at least 6/6 in both eyes, with no refractive error over 3 diopters. All eyes were ophthalmoscopically normal.

Method

The method of testing was based on that of Arden et al. (1962). The subject sat facing and 60 cm from a large viewing box (120 cm \times 180 cm) containing 6 fluorescent tubes which when switched on gave a luminance of 1.00 mill lamberts.

Incorporated in this viewing box were two small red fixation lights positioned to produce a 30° horizontal ocular deviation when looked at alternately. Electrical potentials were recorded with domed silver/silver chloride electrodes containing electrode paste taped to the skin at each canthus with a fifth (the earth electrode) on the forehead. After suitable amplification the electrical potential swings were recorded on direct print photographic paper from a Medelec MS6 oscilloscope.

Each subject had a preliminary practice period of looking alternately from one fixation light to the other at a rate of one swing per second in time with the ticking of a metronome. The room lights were then extinguished and recordings made of eye movements during a 14 second period in every minute over the next 12 min, starting at the 3rd min. At the end of this period the fluorescent tubes in the viewing box were switched on and similar recordings taken over the next 12 min, again starting at the 3rd min.

The recording paper moved at 0.5 cm/sec so that each individual eye move

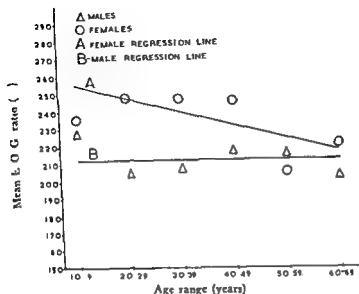


Fig 9

Mean E O G ratios (20 eyes per mean) of 120 normal male and female subjects

Effects of sex and age

Analysis of variance over the whole group showed a significant difference between the sexes ($F = 13.06$ $P < 0.01$) no significant difference for age alone but a significant sex age interaction ($F = 6.6$ $P < 0.05$)

Further analysis on the male (120 eyes) and female (120 eyes) groups separately showed that while there was no significant change with age in the male group there was a significant change with age in the female group ($t = 4.57$ $P < 0.01$)

Table II
Normal limits of E O G ratio

	All	Males	Females	Females < 50 years	Females > 50 years	Males + females > 50 years
Mean	214	213	214	215	210	212
Mean \pm s.d.	154	150	161	160	155	151
Mean \pm s.d.	315	299	330	347	293	290

ment could be identified ensuring that an occasional irregular eye movement would not be included in the final measurements of the amplitude of the saw tooth waveform. The 14 second periods of metronome ticking and the instructions for the changes in illumination interspersed with suitable background music were recorded on a magnetic tape. This tape was played during each test ensuring that all recordings were made at similar time intervals and over the same time period.

Results

The E O G ratios of the 240 eyes are shown in Table I and their frequency distribution histogram is shown in Fig 1A. This histogram appears skewed towards the lower values and the Kolmogorov Smirnov test for goodness of fit indicated that the distribution was significantly skewed ($P < 0.01$). Various arithmetical transformations were tried on the data and the Kolmogorov Smirnov test indicated that the log E O G ratio frequency distribution (Fig 1B) did not differ significantly from a normal distribution curve. Accordingly the statistical analysis was performed on the logarithmically transformed data. In the statistical analysis right and left eyes were treated separately.

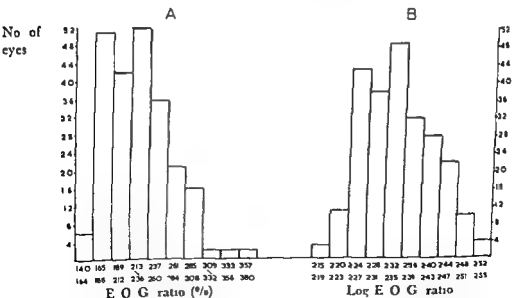


Fig 1

Frequency distribution histograms of F O G ratio before and after logarithmic transformation

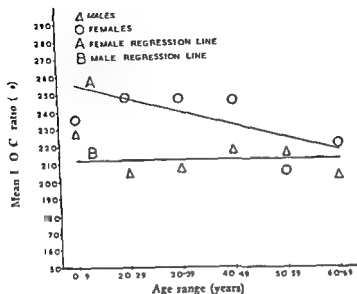


Fig. 2

Mean F O G ratios (% eyes per mean) of 120 normal male and female subjects

Effects of sex and age

Analysis of variance over the whole group showed a significant difference between the sexes ($F = 13.06$, $P < 0.01$) no significant difference for age alone but a significant sex age interaction ($F = 6.6$, $P < 0.05$)

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Mean	214	213	214	215	210	210
Mean s.d.	154	150	161	160	155	151
Mean % s.d.	315	297	330	34	253	290

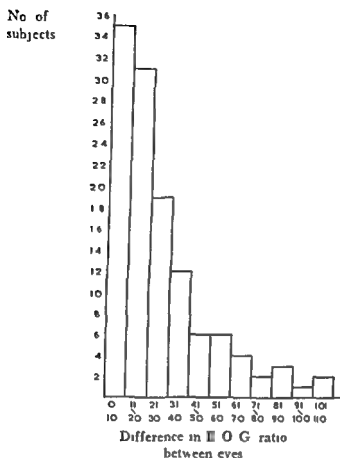


Fig 3

Frequency distribution histogram of difference in E O G ratio between right and left eyes

The nature of the significant differences with age in the female group were investigated by regression analysis. The linear trend was found to be significant ($F = 9.6$ $P < 0.01$) while no significance was found for the higher order functions. Thus there is a significant negative linear correlation between E O G ratio and age ($r = 0.27$ $P < 0.01$) in the female group. The predicted regression line is shown in Fig 2.

Mean E O G ratios

In this series the lowest recorded E O G ratio was 150 (per cent) the highest was 360 and the mean E O G ratio was 224 (to the nearest whole number).

Table II shows the mean E O G ratio the mean minus two standard deviations and the mean plus two standard deviations for various subject groups.

Relationship between right and left eyes

There was no significant tendency for either eye to have a higher E O G ratio although it is apparent from Table I that there is a tendency for right and left eyes to have a similar E O G ratio. The correlation between right and left eyes is significant ($r = 0.756$ $P < 0.01$).

The difference between right and left eyes is shown as a frequency distribution histogram in Fig. 3. This difference was 80 or less in 95% of subjects.

Discussion

The findings of previous workers who have given mean E O G ratios are summarised in Table III.

E O G ratio frequency distribution

The observation that the E O G ratio frequency distribution histogram is skewed towards the lower values was made by Arden & Barrada (1962) who found that a logarithmic transformation normalised the distribution and by Reeser et al. (1970). The latter authors found the logarithmic transformation unhelpful but this may have been due to the second frequency distribution peak in the higher E O G ranges shown in their paper. It seems likely that this second peak is due to the high proportion (31%) of females below the age of 50 years in their series, this group having the highest E O G ratios in the present study.

Effects of sex and age

The presence of a significant difference in F O G ratio between the sexes is a new finding and is of importance in the interpretation of clinical E O G data.

This study suggests that below the age of 50 years E O G ratios are significantly higher in females than in males, whilst after this age female F O G ratios fall to the lower values seen in all males.

The reason for this sex difference is not clear although it is tempting to suggest that some hormonal factor is present in females which can stimulate the metabolic activity of the retinal pigment epithelium but whose secretion falls after the age of 50 years. It is interesting that Miles (1939) in a study

of the ocular standing potential of 56 normal females in three separate age groups found the mean potential to rise from that seen in the age group 10-12 years to a maximum in the age group 17-19 years and then to fall again in the age group 41-65 years

It seems possible that such a hormonal factor might be related to the reproductive process although Kelsey (1967) found no correlation between F O G ratio and stage of the menstrual cycle in a study of repeated E O G recordings on eight normal females aged between 18 and 25 years

A small but significant correlation with E O G ratio and age ($r=0.91$, $P<0.05$) was found by Arden & Barrada (1962) although they described no sex difference. It has not been possible to establish the exact age and sex distribution of the subjects in their study but there were not many subjects over the age of 50 years and there was a definite bias towards female subjects (Arden 1973). The presence of a negative correlation with age is consistent with the female bias in their study while the presence of male subjects and the small number of subjects over the age of 50 years would tend to reduce the apparent significance of such a correlation.

The fact that no other author has described a significant correlation between F O G ratio and age may be due to the very small number of normal subjects over the age of 50 years in the literature (Table III).

Mean E O G ratio

It is of interest to compare the findings of previous studies on mean L O G ratios in the light of the findings of the present study (Table III).

Three studies (Arden & Barrada 1962, Geijer Mannerfelt & Pallin 1968, Reeser et al 1970) found a higher mean E O G ratio than that found in the present study. It is possible that these higher values are due to the definite bias towards female subjects or towards subjects below the age of 50 years shown in these studies.

It is unlikely that the differences in sex distribution are entirely responsible for the higher mean E O G ratio found by Geijer Mannerfelt & Pallin (1968) because this is considerably higher than the mean I O G ratio of any group in the present study. This disparity may be related to the slightly different apparatus and technique used by these authors.

One study (van Lith & Balik 1970) found a lower mean I O G ratio than that found in the present study. This lower value may be due to the higher proportion of male subjects in this group (60%) and their mean I O G ratio of 215 is similar to the mean male F O G ratio of 219 found in the present study.

Table III
Frequency indices of 1 can 1 0 C ratio in normal subjects

Study	Mean F O G ratio	No of eyes	Age range	Sex distribution	Age effect	Correlation between eyes
Arden & Barra la 1960	5.4	52	10-72 years 44 eyes < 50 years 8 eyes > 50 years	-	Significant negative correlation $r = 0.997$ $P < 0.05$	Significant $r = 0.804$ $P < 0.01$
Ceijer Mannerfelt & Pallin 1968	6.5	50	19-9 years	Male 27 Female 58	-	-
Ree et al 1970	4.8	100	00-69 years 80 eyes < 50 years 18 eyes > 50 years	Male 60 Female 80	No significant correlation	Close correlation
van Lith & Balak 1970	6.15	50	01-49 years	Male 28 Female 19	-	-
The present study	5.4	240	10-70 years 160 eyes < 50 years 80 eyes > 50 years	Male 120 Female 120	Significant negative correlation in females $r = 0.97$ $P < 0.01$	Significant $r = 0.756$ $P < 0.01$

Lower limit of normality

Similar considerations of sex and age distribution are relevant when comparing the different published lower limits of normality for E O G ratio

The value of 200 given as the lower limit of normality by Krill (1966) may be high because of the relative youth (average age 27 years) of this group of whom 53% were female (Krill 1972)

The value of 185 given by Arden & Barrada (1962) may be higher than that of the present study because of the definite bias towards female subjects shown in this study (Arden 1973)

The lower limit of normality of 165 found by van Lith & Balik (1970) is lower than that of Krill (1966) and of Arden & Barrada (1962) probably because of the higher proportion of male subjects (60%) in the former study but it is higher than that found in the present study and there is at present no explanation of this difference

The study by Hirata (1969) which gave a lower limit of normality of 150 involved subjects in the age range 16-65 years but more detailed information is not available. This figure would fit in with the present study only if there had been a bias towards male or older subjects

Correlation between right and left eyes

Close correlation in E O G ratio between right and left eyes was found by Arden & Barrada (1962) Geijer Mannerfelt & Pallin (1968) Hirata (1969) and Reeser et al (1970). The degree of correlation found in the present study ($r = 0.756$) is of the same order as that found by Arden & Barrada ($r = 0.904$)

In the present study 95% of subjects showed a difference in E O G ratio of 80 or less between right and left eyes a finding contrary to that of Hirata (1969) who found any difference greater than 92.6 to be abnormal. There is at present no explanation for this disparity

Conclusions

The significant difference in E O G ratio between the sexes suggests that normal limits should be different for males and females. There also appears to be a significant difference between females younger than 50 years and those of 50 years or over

Applying the usual limits of normality ($\text{mean} \pm 2 \text{ s.d.}$) to the logarithmically transformed data provided the values shown in Table II. For simplicity it is suggested that there are only two different ranges. These are

1 All males and females of 50 or more years of age in which the normal range is 150 to 290

2 Females below the age of 50 years in which the normal range is 170 to 312

In both sexes a difference in E O G ratio of more than 80 between right and left eyes is likely to be abnormal

Acknowledgements

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CRITICAL FLICKER FREQUENCY (CFF) IN MAN DURING INDUCED OCULAR HYPERTENSION

I Basic considerations

BY

LENNART BERGGREN

A method for determining critical flicker frequency (CFF) in the central parts of the visual field has been developed. Registration was performed under standard conditions as well as during acute intraocular pressure rise. Intraocular hypertension was induced by dynamometry calibrated by applanation tonometry. With the subject serving as his own control a rather abrupt decrease in CFF was found for central as well as eccentric stimuli at an IOP of about 40–50 mm Hg.

Key words: critical flicker frequency (CFF) – dynamometry – induced intraocular hypertension

The rate of successive light flashes from a stationary light source at which the transition from an appearance of flicker to that of a steady light occurs is called the critical flicker frequency (abbreviated CFF). A flicker experiment can also be performed by determining the point of transition from fusion to flicker. CFF depends on both retinal and cortical function and the relative importance of these functions will vary with different conditions.

A number of experimental procedures are described in physiological psychological and ophthalmological experiments. Different designs and experimental conditions have given rise to difficulties in comparison of data from different

investigations. The instrumentation employed is in general either a light source which is chopped by a rotating sector disc or an electronic apparatus which discharges a gas tube at a high rate. In the latter method the duration of light is constant at every frequency.

The fundamental variables in the instrumentation are stimulus size, light intensity and background illumination. The threshold value depends on the initial rate and whether flicker to fusion or fusion to flicker is employed. CFF also depends on the retinal location of stimulation. Among variables in the test subject which can influence CFF are pupil size, age, state of adaptation, intelligence and influence of drugs. CFF can be influenced by processes in the eye, in the visual pathways or in the cortex. (The reader is further referred to reviews by Simonsen & Brozek 1952, Landis 1954 and Brown 1965).

Investigations have been reported on the variation of CFF in different parts of the retina (Hylkema 1942, 1944) and on the CFF in various eye diseases, particularly glaucoma (Weekers & Roussel 1948, Miles 1950, 1951, Campbell & Rittler 1959). However, the sensitivity of the methods, a sometimes complicated design and the variability of the results under various conditions have led to a rather sporadic use of CFF in ophthalmological diagnosis.

It must be recognized that control of physical variables is not enough. Control of physiological and psychological variables is equally important, as inter- and intraindividual differences are not uncommon. Conclusions based upon comparisons of individual absolute thresholds to standard values from a population sample will therefore be of limited value.

The present and succeeding communications are concerned with determinations of CFF during induced acute increase of intraocular pressure. We have attempted to design a simple instrumentation which is both easily operated by the observer and easily understood by the subject. In order to reduce the influence of variables in instrumentation or subject which have made the interpretation of previous results difficult, the test subject serves as his own control. This means that the values of the subject during induced ocular hypertension are compared to his own values under standard conditions. The aim has been to develop a test of susceptibility to raised intraocular pressure in the individual eye.

Material

In the development and testing of the method a test group comprised of three eye healthy subjects, 4-44 years of age, was used. Their blood pressures were normal (15-110 mm. Hg).

Methods

Photostimulator A photostimulator from Grass Medical Instruments Quincy Mass USA was used. The frequency range of 5–100 flashes/sec is continuously variable. Flash intensity can be varied in five steps (with the ratios 1, 2, 4, 8 and 16). The approx. max. flash intensity is 15 500 000 candle power. The flash lamp type is PST 2 with a flash duration of 10 microsec.

General method The gas discharge lamp is mounted in a metal housing. Exchangeable black discs with either a central aperture or one to four eccentric apertures could be inserted in the front panel. Two layers of non-transparent plastic sheet (Steri Drape) are used as diffusing material covering the apertures. The eccentric apertures are symmetrically positioned at 13° or 18° from the central fixation point of the subject. The number of stimuli simultaneously exposed can be varied from one to four. By rotating the disc with eccentric apertures, different parts of the central visual field can be tested with flickering light stimuli. The areas which were tested were 1.5° , 3.0° and 4.5° . The subject sits 33 cm in front of the disc with test targets (Fig. 1). The flash rate is changed by hand by the observer at a steady and fixed rate. The subject registers the CFI-threshold by knocking on the instrument table. CFI has been determined using both the fusion to flicker method and the flicker to fusion method. Discontinuous changes of rate of flashes were also tested. The influence of the light intensity on CFI determinations were also studied.

Artificial increase of intraocular pressure Two methods of increasing the IOP by dynamometry were compared. A dynamometer *ad modum* Brillart was

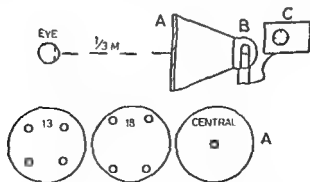


Fig. 1

CFF instrumentation. A: The discs with central and eccentric apertures. B and C: The photostimulator with flash tube.

applied temporally outside the eye lid. The force in grams is converted to mmHg by comparison with applanation tonometry. Suction dynamometry was applied using a hemispherical plastic suction cup with an inner diameter of 10 or 12 mm. The suction cup was applied to the conjunctiva at the temporal limbus and suction was performed using a vacuum pump. The negative pressure was converted to mmHg by comparison with applanation tonometry. The technique was similar to that used by Galin et al (1969).

Applanation tonometry

The experiments were calibrated by conversion of the dynamometry readings used in CFF tests to applanation values in mmHg. Conventional applanation tonometry according to Goldmann was used prior to or directly after the CFF experiments.

Results

Light Intensity

Light intensity influences CFF (Brown 1965). Using step 1 on the photostimulator a CFF was obtained which was significantly lower than the CFFs recorded using higher intensities. Steps 8 and 16 which were maximum intensities caused a considerable decrease in burning time of the gas discharge lamp. Therefore in succeeding experiments step 2 on the photostimulator was generally used.

Stimulus size

The size of the stimulus influences CFF (Brown 1965). An area of 1.5° gave rise to significantly lower value than the areas 3.0° and 4.5° . In succeeding experiments a test area of 3.0° was generally used. It was considered to be the smallest area which gave reliable results in the analysis of the CFF function in the central parts of the visual field.

Location of stimulus

Using a stimulus size of 3.0° which is movable around the 13° and 18° isopter ($11.5 - 19.5^\circ$) gave a satisfactory covering of particularly the Bjerrum area in the central visual field (Fig. 2).

Number of simultaneously exposed stimuli

An analysis of the visual field from 11.5° to 19.5° can be performed either by exposure with one stimulus at a time in different meridians or by exposure of

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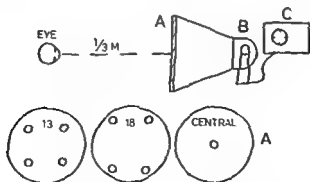


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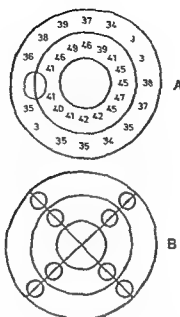


Fig 2

Top CFF levels in different parts of the central visual field of the left eye of a normal subject A 3° target was used in the 15° and 18° isopters
 Bottom Schematic drawing of the rotatable discs and their 3 apertures

several areas simultaneously. The first method is more exact but it is very time consuming and thus unsuitable as a routine clinical method. By using the latter method the gain of time depends on the number of areas which may be recorded at one and the same exposure. A complete analysis concerning location and CFF frequency of four simultaneously exposed stimuli generally proved to be beyond the ability of even a trained subject. The analysis of four symmetrically placed flickering targets was therefore limited to recording the frequency of the best area (when the first spot begins to flicker) and the "worst" area (when all spots are seen as flickering). The first method was used in analysing the CFF frequencies in different parts of the Bjerrum area in normal subjects. The second method was used in the dynamometry studies which demanded short time experiments. Both methods in their present design are considered unsatisfactory as clinical routine methods.

Flicker method

Experiments with flicker to fusion regularly resulted in lower CFF values than when fusion to flicker was used. The ability and/or the difficulty to respond

to the threshold value in the two methods can be determined by the subject's opinion or by measuring the variation (in general up to ± 2 flashes/sec). In the trained subject there was hardly any difference. In the present report fusion to flicker with continuous decrease of rate of flashes was used in the following. The problem will be further dealt with in a succeeding paper.

CFF in the central visual field

An analysis using the present instrumentation has confirmed the results of previous investigators (Hylkema 1942, 1944; Weekers & Roussel 1948; Miles 1950, 1951; and Campbell & Rittler 1959). Variations in CFF exist in the normal visual field. The location of maximum CFF is parafoveal and the CFF then decreases towards the periphery. Besides these differences, variations were also found in different quadrants in the normal visual field. These variations are probably due to the location of the large vessels in the eye ground. An example of CFFs in different parts of the Bjerrum area from 11.5° to 19.5° using the method with only one stimulus at a time is given in Fig. 2.

Dynamometry

Preliminary experiments showed that the suction cup method was technically superior and gave more reproducible values compared to standard Baillart

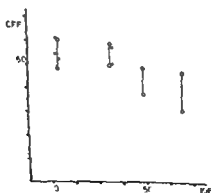


Fig. 3

CFF at different IOP levels induced by dynamometry. Black dots represent values from three normal subjects, 4 spots of 5 in the 45° , 15° , 0° and 315° meridians and 15 in the fixation point are simultaneously exposed. At each IOP level the subjects select the best and worst spot. Open dots represent mean values.

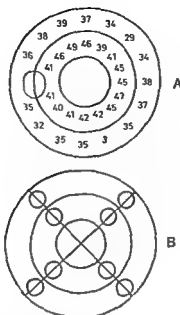


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at the same time. As mentioned above, a further analysis concerning the flicker frequency of all the spots and their location in the visual field proved to be too difficult. The results from the three subjects at normal and artificially raised IOPs are presented in Fig. 3. With four stimuli at 13° the figure shows that the CFFs are fairly stable up to about 40 mmHg and then decrease. Experiments with four spots around 18° gave lower CFF values but were otherwise similar.

Changes in CFF with time during dynamometry

In the experiments described above, CFF during dynamometry was related to the individual applanation pressure which was obtained by a defined pressure of the dynamometer. However, the measurement of CFF during dynamometry is in fact a tonography experiment and the intraocular pressure is decreasing. This error seems often to be overlooked in standard dynamometry; for instance, to study this factor the following experiment was performed. The dynamometer was applied at a defined level and the CFFs were registered every minute during five minutes. Applanation tonometry was performed later under the same experimental conditions. In this type of experiment only one central stimulus of 9.0 was used.

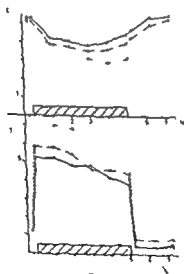


Fig. 5

Top CFF values in a normal subject during dynamometric load for 5 minutes. Bottom IOP levels measured by applanation tonometry during the same period. IOP levels from initially 5 mmHg.

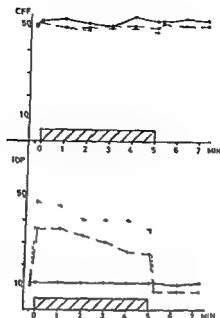


Fig 4

Top CFF values in a normal subject during dynamometric load for 5 minutes
 Bottom IOP levels measured by applanation tonometry during the same period
 IOP levels from initially 12-18 mm Hg

dynamometry. However, in connection with CFF measurements the method turned out to be too uncomfortable and had to be abandoned. The Baillart dynamometer is easy to handle and apply. By this method it is questionable, however, whether defined changes in the plunger load give accurate and reproducible changes in IOP obtained from conversion tables. This technical weakness was reduced in the present experiments by direct applanation tonometry of the individual dynamometer loaded eye. The dynamometer experiments were thus run as follows: the Baillart dynamometer was applied at a defined level and CFF determined. On another occasion the applanation pressure was measured with the dynamometer in the same position and using the same pressure.

Experiments with several simultaneously exposed stimuli during dynamometry

Fusion to flicker and four simultaneous stimuli were used. The test spots were either 13° or 18° from the fixation point and placed in the 45° , 135° , 225° and 315° meridians. The first response from the subject is noted when the first stimulus begins to flicker ("best" spot) and the next notation is made when all four stimuli flicker ("worst" spot). Sometimes all spots were observed to flicker.

Discussion

In previous investigations (Gafner & Goldmann 1955 Drance 1962) the individual susceptibility to raised intraocular pressure has been studied. Gafner and Goldmann investigated the appearance of sciascotoma and Drance the appearance of Bjerrum scotoma during dynamometry. In the present report CFF determinations during acute intraocular pressure increases were chosen as a method for testing the central parts of the fundus of the eye.

The reliability of a subjective clinical method depends totally on the test subject's reability to cooperate. It is essential that the subject make quick decisions and simple responses. The transition from fusion to flicker (or vice versa) is not a sharply defined threshold. The subject first observes separate light flashes of a flickering light with gradually increasing frequency. This is followed by a coarse flickering which then passes into a fine tremulous flickering after which the appearance of fusion occurs (Parsons cited 1965). The difficulty of establishing CFF was reduced by letting the subject determine his own standard value and then comparing this with his own values obtained during intraocular pressure rise instead of attempting to establish an absolute CFF. An attempt to quickly explore the central visual field i.e. the Bjerrum area by several simultaneously exposed stimuli was partly a failure since it generally proved to be beyond the ability of even a trained subject. With central fixation it was found to be very difficult to separate several flickering eccentric lights. It was considerably easier to analyse a single central flickering light. The results obtained with eccentric and centric flickering lights were similar. The CFF level was relatively unaffected by acute intraocular pressure rises up to about 40 mmHg in the normal subjects tested. Above this limit a sudden drop in CFF occurred. This suggests an interference with the vascular supply. A succeeding report will deal with a more thorough analysis of the demonstrated CFF drop at induced IOI rise. The instrumentation is further developed to a technically more satisfactory method.

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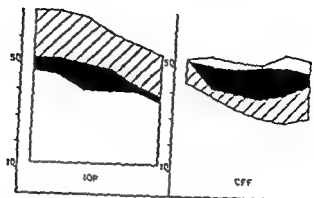


Fig 6

Schematic drawing of results from Figs 4 and 5. Dynamometry time 5 minutes. Open, black and striped areas show IOP regions and corresponding CFF regions. Open areas show moderately elevated IOP with no change in CFF. Black areas show critical IOP levels where a significant decrease in CFF begins to occur. Striped areas show high IOP levels which cause a further CFF decrease.

A representative experiment from γ series performed on one of the subjects is presented in Figs 4 and 5. The following can be extracted from these figures:

- The tonographic effect at different dynamometer levels is clearly seen on the time - pressure curve.
- In agreement with the previous experiments using eccentric targets it is noted that the central CFF is also fairly stable up to an intraocular pressure of 40-50 mmHg.
- When the mean pressure exceeds approximately 50 mmHg a relatively marked drop in CFF occurs.
- A further increase of IOP causes only a moderate further decrease in CFF.
- It can be noted that as the intraocular pressure decreases with time during dynamometry there is a tendency to recovery in CFF.

It was thus found that the decrease in CFF during acute intraocular hypertension does not seem to be a gradual process but occurs fairly suddenly at a certain pressure level. The findings are further illustrated graphically in Fig 6. Moderate increases in IOP during γ minutes do not significantly affect CFF (unfilled areas). In the critical region of IOP a significant decrease in CFF is induced (black areas). High IOP levels cause a moderate further decrease in CFF (striped areas). Still further increases in IOP give rise to visual black out and make CFF determinations impossible. Fig 6 also shows that the fall in CFF is most marked during the first minute.

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CRITICAL FLICKER FREQUENCY (CFF) IN MAN DURING INDUCED OCULAR HYPERTENSION

II Technique and analysis of a normal group

BY

LENNART BERGGREN

Using a new technique twelve subjects with healthy eyes 44-44 years of age were studied by CFF and IOP determinations during acute intra ocular pressure rises induced by dynamometry. An abrupt significant decrease in CFF was noted above 40 mmHg. There was no evidence that the CFF level during dynamometry was affected by changes in pupil size, astigmatism or refractive error. It is suggested that the cause of the decrease in CFF may be due to vascular changes in parts of the choroidal circulation. The apparatus has been designed in order to make future clinical use possible. When used for testing normal subjects the apparatus has been shown to be easy to handle and requires only reasonable cooperation from the test subject. The investigation takes only a few minutes.

Key words: choroidal circulation - critical flicker frequency - dynamometry - induced ocular hypertension - retinal circulation

In a previous paper (Berggren III 3) preliminary results were presented showing that the critical flicker frequency (CFF) decreased when the IOP was raised to about 40-50 mmHg. Some variables in the instrumentation as well as

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In a previous paper (Berggren 1973) preliminary results were presented showing that the critical flicker frequency (CFF) decreased when the IOP was raised to about 40-50 mmHg. Some variables in the instrumentation as well as

in the subject were also studied. In the present report the validity of the results is tested on a larger experimental group. Of particular interest has been to study whether the application of the dynamometer affected the eye in some way which might influence the CFF threshold. Refined instrumentation permitted CFF thresholds to be read more easily as well as permitted determinations of CFF and applanation tonometry on the same occasion.

Material

The experimental group comprised twelve subjects of both sexes 24-44 years of age with clinically healthy eyes.

Methods

Photostimulator and flash lamp. A photostimulator from Grass Medical Instruments Quincy, Mass. USA was used. The frequency range 5-100 flashes/sec is continuously variable. Flash intensity can be varied in five steps (with ratios of 1, 2, 4, 8 and 16). The approximate maximum intensity is 1 500 000 candle power. The flash lamp type is PST 2 with a flash duration of 10 microsec.

The front glass cover of the conventional flash lamp is replaced by a grey painted metal disc. The disc has a central aperture 52 mm in diameter. The aperture is covered by an opalescent plastic diffusion disc of 2.5 mm thickness.

General method

The basic principles of the method have been outlined in a previous report (Berggren 1973).

In the present set up the subject sits in a Haag Streit slit lamp microscope provided with a Goldmann tonometer. The flash lamp with its central aperture giving a central flickering stimulus of 3.0 is placed in front of the eye of the subject and at a distance of one meter.

The applanation IOP is measured. A lens = the refractive error of the subject + 1 D is then placed in front of the eye. Standard CFF thresholds are determined and the mean from a standard series of 9 determinations is used. CFF is generally measured from flicker to fusion starting with 10 flashes/sec. The subject indicates that his CFF threshold has been reached by knocking on the instrument table.

The Baillart dynamometer with a pre-chosen pressure is applied temporally

outside the eye lid while the subject sits with his head resting in the head frame of the microscope. The IOP is measured. After the dynamometer has been applied for one minute three CFF determinations are recorded and the mean is noted. The IOP is again measured with the dynamometer in position. The mean of the two IOP determinations is used. The whole procedure takes less than 2 minutes. After a couple of minutes the test can be repeated at another pressure level. A maximum of two dynamometry experiments were performed on one and the same occasion. In the CFF/IOP determinations the subject serves as his own control.

Studied variables

The following parameters were investigated under standard conditions and during dynamometry: pupil size, refractive error and corneal astigmatism, as well as a comparison of the flicker fusion method and the fusion flicker method. The influence on CFF by varying the refractive state of the eye was also studied.

Results

In the first experiments the method was tested with respect to the variables mentioned above. The determinations from the normal test group under standard and dynamometry conditions are summarized in Table I. The Baillart dynamometer was applied using a pressure of 30-40 mmHg. This is the upper limit value used in these experiments and gave an initial IOP rise to about 40-60 mmHg. It might be argued that changes in CFF might be due to anatomical changes in the eye caused by dynamometer pressure. It is evident from the results in Table I that the variables studied were unaffected by the application of the dynamometer.

Pupil sizes show only moderate individual changes with a maximum increase in the diameter of 0.4 mm. The mean change is negligible.

Determinations of corneal astigmatism using the Javal ophthalmometer on the Haag Street double table show only small changes during dynamometry compared to standard conditions. The maximum variation is ± 1 D. The mean change is negligible.

The refractive error changes very little during dynamometry compared to standard conditions. A slight myopia of up to -1.0 D is sometimes noted. The mean change is insignificant.

In the previous communication trained subjects seemed subjectively to prefer the fusion flicker method to the flicker fusion method if they expressed a preference. However, in the present study the majority of the inexperienced

in the subject were also studied. In the present report the validity of the results is tested on a larger experimental group. Of particular interest has been to study whether the application of the dynamometer affected the eye in some way which might influence the CFI threshold. Refined instrumentation permitted CFI thresholds to be read more easily as well as permitted determinations of CFI and applanation tonometry on the same occasion.

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Methods

Photostimulator and flash lamp. A photostimulator from Grass Medical Instruments Quincy Mass. USA was used. The frequency range 5-100 flashes/sec is continuously variable. Flash intensity can be varied in five steps (with ratios of 1, 2, 4, 8 and 16). The approximate maximum intensity is 1500 000 candle power. The flash lamp type is PST 2 with a flash duration of 10 microsec.

The front glass cover of the conventional flash lamp is replaced by a grey painted metal disc. The disc has a central aperture 52 mm in diameter. The aperture is covered by an opalescent plastic diffusion disc of 2.5 mm thickness.

General method

The basic principles of the method have been outlined in a previous report (Berggren 1973).

In the present set up the subject sits in a Haag Streit slit lamp microscope provided with a Goldmann tonometer. The flash lamp with its central aperture giving a central flickering stimulus of 30° is placed in front of the eye of the subject and at a distance of one meter.

The applanation IOP is measured. A lens = the refractive error of the subject + 1 D is then placed in front of the eye. Standard CFI thresholds are determined and the mean from a standard series of 9 determinations is used. CFI is generally measured from flicker to fusion starting with 10 flashes/sec. The subject indicates that his CFI threshold has been reached by knocking on the instrument table.

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Table I

Determinations of pupil size, corneal astigmatism and refractive error in normal subjects under standard and dynamometry conditions. CFF determinations are also recorded at varying refractive states by using fusion to flicker as well as flicker to fusion.

Sbj	t/y	Age	Pupl W		C r n A stig D		R f		CFF Flk h	St nd	CFF Flk h Pu ton	St nd	CFF		t	w h	
			B f	Aft	B f	Aft	B f	D					Aft	1			2
1	D R	d	27	4 0	4 0	0 5 90	0 5 90	+0 75	+0 5	37	1 5	38	3 0	40	43	41	38 39
2	G L	d	28	5 0	5 0	1 0 90	0 5 90	+0 5	0 0	52	4 0	42	1 4	40	41	45	39 38
3	A h	d	28	5 2	5 4	1 0 90	1 0 90	0 0	1 0	37	2 1	44	1 0	37	42	43	33 35
4	I B	d	28	3 8	3 9	1 0 70	1 0 70	5 0	5 0	35	1 5	43	1 4	33	47	38	45 44
5	B J	d	24	5 3	5 5	0 5 90	0 0	0 0	0 0	65	3 2	48	1 4	38	50	38	50 48
6	B W	d	28	5 8	6 2	1 0 80	0 5 80	+0 5	+0 5	48	1 3	54	1 9	38	50	53	51 51
7	C W	d	27	5 0	5 0	2 0 90	2 0 90	+0 5	+0 5	47	3 7	48	1 4	47	50	50	48 47
8	H L	d	36	4 3	4 3	1 0 85	0 5 85	0	0 0	58	1 0	49	1 3	38	39	39	37 3
9	J B	d	33	4 0	4 0	1 5 90	2 0 90	+0 5	+0 5	28	1 0	38	0 9	37	39	37	35 34
10	M T	d	33	4 4	4 7	0 5 90	1 0 90	0 75	0 75	48	1 1	49	1 2	38	42	41	38 41
11	K E	d	24	5 5	5 5	0 5 90	1 0 90	5 0	5 5	55	0 9	39	1 0	40	41	38	39 40
12	L B	f	44	5 0	5 2	0 5 90	0 0	3 0	3 5	62	2 8	44	1 4	42	47	45	44 43
N			30	4 8	4 9	1 0 D	0 75 D	0 25 D	37	1 7	45	1 4	4	44	44	41 41	

subjects preferred the flicker fusion method. The individual mean standard deviation was ± 1.4 flashes/sec for flicker fusion and ± 1.7 for fusion flicker. The group mean standard deviations are considerably higher ± 5.8 and ± 4.5 respectively. These large standard deviations speak against the use of a group mean as a suitable standard for evaluation of the individual CFF values. The low individual standard deviations support the use of each subject as his own control. In the following experiments flicker fusion was the method employed.

Moderate changes of the refractive state by adding from +4.0 D to -4.0 D to the refractive error showed that CFF changed very little in this experimental group of individuals who possessed accommodative ability. It was sometimes noted that uncorrected myopics showed a higher CFF level compared to their own CFF levels obtained using full correction. This is probably explained by the larger retinal image and accordingly larger stimulus area in the uncorrected eye. To exclude accommodation a +1 D lens was always added to the corrective lens.

In another type of experiment IOP and CFF determinations were first performed under standard conditions and then at least two CFF/IOP determinations were performed during dynamometric pressure load. Two pressure levels

Table II

CFF IOP determinations in normal subjects at different IOP levels induced by dynamometry

Subject/eye	Induced IOP	CFF/IOP			
		Dynamometer + loaded eye			
		IOP 21 30	IOP 31-40	IOP 41 50	IOP 51 60
1 D R d	44/12		44/35		44/53
2 G L d	43/14		42/35	38/50	
3 A H dx	41/14	40/30		35/43	
4 T Y dx	43/12		44/38	43/48	
	44/16				38/53
5 B J dx	49/10	51/30		38/41	
6 B M dx	49/13		47/33	41/46	
7 G V d	51/13		49/40		
	49/15			45/47	
8 M L d	44/12		43/40	37/48	
9 J E dx	37/13		36/36		33/54
10 W T d	45/10		43/31	26/45	
11 R E d	42/15			38/47	
	43/14		43/33		
12 L B i	49/16		50/32		42/32

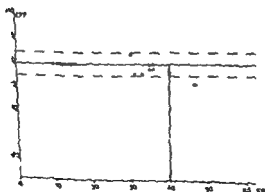


Fig. 1

CFF IOP determinations in normal subjects (same group as in Tables I and II). CFFs and IOP at normal conditions are taken as zero. Differences in flashes/sec from zero at different IOP levels are noted. Broken line represent ± 3 SEM from zero value.

were of particular interest just below the "critical" level where a CFF drop can be expected and just above this level i.e. in the range of 30 to 60 mmHg

CFF was measured after one minute of dynamometry. In the previous report it was noted that IOP decreased more rapidly during the first minute. The mean of initial IOP (onset of dynamometer) and final IOP (after the CFF determinations after one minute) was used as the mean IOP during dynamometry. The error due to non linear decrease of IOP is at most a few mmHg.

In Table II the absolute values are recorded. The individual differences revealed in this normal test group further exemplify the limited value of comparing individual absolute figures to the mean values from a normal sample. The results are illustrated graphically in Fig. 1. The absolute standard values are recorded as zero values and the differences from zero during dynamometry are calculated. Dashed lines on both sides of the zero line represent ± 3 SEM. It is obvious that pressures below 40 mmHg do not affect CFF. A pressure level above 40 mmHg however significantly lowers CFF. In two cases considerable decreases were noted and the subjects were near visual black out.

All subjects had normal blood pressure. The mean systolic/diastolic ratio was 120/80 (and the ranges were 135-110/95-70). The subject who tolerated the highest IOP rise without a decrease in CFF had a blood pressure (110/70) which did not differ from those (110/70 and 120/80) who had a considerable decrease with only a slight IOP rise.

Discussion

There was no evidence that the decrease in CFF recorded at higher IOPs was due to any cause other than the pressure rise itself. The sudden decrease in function reflected in the CFF determinations is more suggestive of an effect on the vascular supply than for example an interference with metabolic processes in the receptors.

The effects of acute IOP rises on the retinal and choroidal circulation have been studied by several investigators. Hayreh (1969, 1972) has extensively studied the circulation in the monkey during artificial intraocular pressure rise. His anatomic and angiographic studies showed that the choroidal circulation is the first to suffer. During acute increase in IOP the vessels in the prelaminar region were most susceptible to obliteration. Slightly less susceptible to obliteration was the peripapillary choroid and least susceptible the remainder of the choroidal circulation. In Hayreh's experiments the retinal circulation was not susceptible to obliteration unless the IOP was above the central artery pressure. However fluorescein angiograms in the farm pig showed that in

creased intraocular pressure slowed filling in both retinal and choroidal vessels (Dollery et al 1968) Infrared absorption angiography using indocyanine dye has showed that at extremely high IOP retinal circulation was obliterated while an attenuated choroidal circulation persisted (Flower 1972)

Alm & Bill (1972 1973) have recently shown that a moderate increase in eye pressure in monkeys causes the blood flow in the prelaminar part of the optic nerve to fall parallel with that in the choroid In cats and monkeys the blood flow has been shown to be 20 times higher through the choroid than through the retina and the retinal vessels were calculated to supply only $\frac{1}{3}$ of the oxygen consumed by the retina The blood flow through the central part was much higher than that through those in the periphery The blood flow through the choroid lacks autoregulation When IOP is increased the blood flow is proportionately reduced Similarly the prelaminar part of the optic nerve head also lacks autoregulation which might explain the susceptibility of the optic nerve head to increased IOP A moderate increase in IOP reduced blood flow in the choroid and optic nerve head but there was no decrease in the retinal blood flow High intraocular pressures reduced blood flow in all intraocular tissues (Bill 1973 Alm & Bill 1973) Gafner & Goldmann (1955) have suggested that when IOP is raised the blood flow in the optic nerve head is shunted away to the retrobulbar part of the optic nerve The importance of reduced blood flow is stressed by both theories

Decrease in transmural pressure affects the equilibrium between transmural pressure vascular tension and vessel diameter and might result in an abrupt closure of a previously open vessel The pressure level at which blood flow stops is called the critical closing pressure (Burton 1951 Burton & Yamada 1951 Nichol et al 1951) In the average vascular bed tissue pressure is assumed to be close to zero Transmural pressure changes are thus in general caused by arterial pressure changes The vascular system in the eye is rather unique in the sense that the surrounding pressure (IOP) has an appreciable and variable magnitude This means that transmural pressure changes can be produced either by changes in vascular pressure or by changes in IOI

In a series of papers Best (also Blumenthal et al (1969 1971) have reported different techniques to study the hemodynamics in the eye In *in vitro* perfusion experiments of the ophthalmic artery in the rabbit flow was stopped when the perfusion pressure was lowered to a level 6 mm Hg above the intraocular pressure level The results were thought to be due to critical closure of intraocular vessels Fluorescein angiographies in man during dynamometry showed that after an acute increase in intraocular pressure the peripapillary choroidal vessels and optic disc vessels reopened at an average IOI of 60 mm Hg It was suggested that the choroidal vessels might have a higher tension than

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CIF was measured after one minute of dynamometry. In the previous report it was noted that IOP decreased more rapidly during the first minute. The mean of initial IOP (onset of dynamometer) and final IOP (after the CFF determinations after one minute) was used as the mean IOP during dynamometry. The error due to non linear decrease of IOP is at most a few mmHg.

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Decrease in transmural pressure affects the equilibrium between transmural pressure, vascular tension and vessel diameter and might result in an abrupt closure of a previously open vessel. The pressure level at which blood flow stops is called the critical closing pressure (Burton 1951, Burton & Yamada 1951, Nichol et al 1951). In the average vascular bed tissue pressure is assumed to be close to zero. Transmural pressure changes are thus in general caused by arterial pressure changes. The vascular system in the eye is rather unique in the sense that the surrounding pressure (= IOP) has an appreciable and variable magnitude. This means that transmural pressure changes can be produced either by changes in vascular pressure or by changes in IOP.

In a series of papers Best, Galin, Blumenthal et al (1969, 1971) have reported different techniques to study the hemodynamics in the eye. In *in vitro* perfusion experiments of the ophthalmic artery in the rabbit flow was stopped when the perfusion pressure was lowered to a level 6 mm Hg above the intraocular pressure level. The results were thought to be due to critical closure of intraocular vessels. Fluorescein angiographies in man during dynamometry showed that after an acute increase in intraocular pressure the peripapillary choroidal vessels and optic disc vessels reopened at an average IOP of 60 mm Hg. It was suggested that the choroidal vessels might have a higher tension than

were of particular interest just below the "critical level where a CFF drop can be expected and just above this level i.e. in the range of 50 to 60 mmHg.

CFF was measured after one minute of dynamometry. In the previous report it was noted that IOP decreased more rapidly during the first minute. The mean of initial IOP (onset of dynamometer) and final IOP (after the CFF determinations after one minute) was used as the mean IOP during dynamometry. The error due to non linear decrease of IOP is at most a few mmHg.

In Table II the absolute values are recorded. The individual differences revealed in this normal test group further exemplify the limited value of comparing individual absolute figures to the mean values from a normal sample. The results are illustrated graphically in Fig. 1. The absolute standard values are recorded as zero values and the differences from zero during dynamometry are calculated. Dashed lines on both sides of the zero line represent ± 3 SEM. It is obvious that pressures below 40 mmHg do not affect CFF. A pressure level above 40 mmHg however significantly lowers CFF. In two cases considerable decreases were noted and the subjects were near visual black out.

All subjects had normal blood pressure. The mean systolic/diastolic ratio was 120/80 (and the ranges were 130-110/85-70). The subject who tolerated the highest IOP rise without a decrease in CFF had a blood pressure (110/70) which did not differ from those (110/70 and 120/80) who had a considerable decrease with only a slight IOP rise.

Discussion

There was no evidence that the decrease in CFF recorded at higher IOPs was due to any cause other than the pressure rise itself. The sudden decrease in function reflected in the CFF determinations is more suggestive of an effect on the vascular supply than for example an interference with metabolic processes in the receptors.

The effects of acute IOP rises on the retinal and choroidal circulation have been studied by several investigators. Hayreh (1969, 1972) has extensively studied the circulation in the monkey during artificial intraocular pressure rise. His anatomic and angiographic studies showed that the choroidal circulation is the first to suffer. During acute increase in IOP the vessels in the prelaminar region were most susceptible to obliteration. Slightly less susceptible to obliteration was the peripapillary choroid and least susceptible the remainder of the choroidal circulation. In Hayreh's experiments the retinal circulation was not susceptible to obliteration unless the IOP was above the central artery pressure. However fluorescein angiograms in the farm pig showed that in

lacks autoregulation and to a lesser degree with the retinal circulation which is effectively autoregulated. Critical closure of some intraocular vessels might be involved. The critical site of asphyxia seems to be in the retinal ganglionic cell layer. The present experiments show a rather sudden drop in CFF frequency at 40–50 mm Hg and the visual black outs noted in two cases are compatible with these views. It must be pointed out that the present findings are obtained from acute experiments in normal human beings. At present one cannot draw any conclusions regarding to what extent these results are applicable to chronically raised intraocular pressure, especially in elderly persons with defective circulation. However, CFF determinations during induced ocular hypertension in eye diseases such as glaucoma and macular degeneration in which circulatory disturbances may be an etiological factor should be of particular interest. Succeeding experiments will deal with these problems.

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retinal vessels of corresponding size. Studies of ocular volume changes after carotid occlusion in the rabbit showed that for moderate IOP increases there is a semilogarithmic relationship between the ocular volume changes and perfusion pressure or tonometric pressure. At intraocular pressures above 50 mm Hg the relationship no longer holds due most probably to critical closure of intraocular vessels.

Visual function during acute intraocular pressure rise has most frequently been studied by determination of the visual fields during dynamometry. Development or progress of visual field defects have been described by Drance (1962) and Jaeger et al (1964). Sciascotometry *ad modum* Gafner & Goldmann (1955) is another method for studying the sensitivity of the visual fields to an acute intraocular pressure rise. These examinations are elaborate and time consuming and require good cooperation from the patient.

Reduction in perfusion pressure by lowering the mean arterial pressure instead of increasing the intraocular pressure produces similar effects on circulation in the eye and on the visual fields. The well known black out phenomenon occurring in airplane pilots subjected to positive g forces have experimentally been studied by Duane (1954). The observer studied the fundus while the subject experienced positive g in a human centrifuge. At about 4 g objective initial arteriolar pulsations occurred a few seconds before subjective dimming of vision. This was followed by objective arteriolar exsanguination and subjective black out. CFF levels were influenced only at accelerations that gave dimming of vision (Keighley et al 1951). Rapid progress of visual field defects in glaucomas where the blood pressure has been suddenly lowered are described by Harrington (1969).

Registration of the electroretinogram during acute increase of intraocular pressure has given some information of the critical site of the asphyxial block in the retina. The supernormal ERG found in acute glaucoma is explained by Karpe & Wulffing (1961) to be due to retinal stasis. An acute increase in intraocular pressure induced by a dynamometer device or by connecting a cannulated eye to a pressure reservoir results in a decrease in the b wave potential (Burian 1953, Wulffing 1963, Karlberg et al 1968). Fujino & Hama-saki (1967) established that consistent changes in ERG were obtained only when the intraocular pressure exceeded the diastolic pressure. In recordings of the ERG and the optic nerve potentials during high intraocular pressures Noell (1951) showed that the asphyxial block of retinal excitation occurs initially in the ganglionic cell neuron and optic nerve layer. This is followed by an impairment of excitation within the outer layer (decline of b wave).

Thus from the studies discussed above it seems likely that an acute moderate intraocular pressure rise interferes mainly with the choroidal circulation which

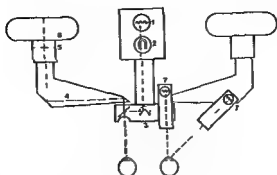


Fig 2

- | | |
|---|---|
| 1 Incandescent lamp illumination | 5 Secondary filter |
| 2 Electronic flash tube | 6 Robot motor camera |
| 3 Light distribution tube with primary filter | 7 Focusing lamps (shown on the right side only) |
| 4 Right angled objective tube | |

Diagram showing the paths of light rays for the adjustment of the cameras by incandescent lamp illumination (1-3) for electronic flash illumination of the irides (2-3) for photography (4-6) and for the focusing lamps (7-7)

As the size of the cameras prevents them from being placed so that the distance between them is equal to the interpupillary distance in the patient each camera is fitted with the special objective which is otherwise used for slit lamp photography. These objectives are mounted in a right angled tube with a front prism but modified so that the tubes can be rotated in the frontal plane and an intermediary lens is inserted to compensate for the short object distance.

In order to avoid undesirable reflexes from the corneae the usual prism in the illumination tube of the photo slit lamp has been replaced by a T shaped tube placed below the right angled objective tubes. Each arm of this T tube has an opening directed forwards and upwards through which the light from both the incandescent lamp and the electronic flash passes. The illumination is focused on the patient's corneae by means of an adjustable mirror arrangement in the tube (3 in Fig 2). The activating blue interference filter is inserted in the vertical part of the T tube.

Each camera is provided with a device for optical registration of the time and exposure number - reflected from a timepiece and film counter built into the desk - and of previously recorded patient data. A green yellow secondary filter is inserted in the holder of each camera.

The generator used for retinal angiography supplies current across a foot operated switch to the two cameras the incandescent lamp and the electronic

(Hollenhorst & Kearns 1961 Pemberton & Britton 1964) arm to retina circulation time (Gilland et al 1965 David et al 1966) corneal pulsation (Nornes et al 1971) tonography (Miles et al 1967 Solis et al 1972) isotope angiography (Dimast et al 1972) retinal fluorophotometry (Trokkel 1971 Winkelmann et al 1971, Niesel & Grassmann 1972) and pressure measurements in the ophthalmic artery (Borras et al 1969)

The experience gained after the introduction of fluorescence angiography of the iris (Jensen & Lundbeck 1968 Bruun Jensen 1969 Briggensen 1969 1971) suggested that it would be possible to overcome the complex technical difficulties encountered in simultaneous angiography of the fundi by studying the optically far more accessible irides instead. The method devised for this purpose has proved so simple that it can be used in out patients.

In principle the arrangement used consists of two synchronized automatic cameras with a common electronic flash. Each of the two recording cameras (Robot Motor Recondor 3b BE) is mounted on an adjustable sliding plate on a wooden platform fixed to the mobile underframe of the Zeiss photo slit lamp.

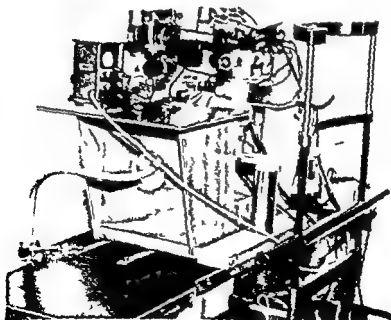
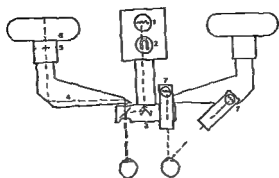


Fig 1

Synchronized cameras for simultaneous fluorescein angiography of both irides



Fig

- | | |
|---|---|
| 1 Incandescent lamp illumination | 5 Secondary filter |
| 2 Electronic flash tube | 6 Robot motor camera |
| 3 Light distribution tube with primary filter | 7 Focusing lamps (shown on the right side only) |
| 4 Right angled objective tube | |

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In order to avoid undesirable reflexes from the cornea the usual prism in the illumination tube of the photo slit lamp has been replaced by a T shaped tube placed below the right angled objective tubes. Each arm of this T tube has an opening directed forwards and upwards through which the light from both the incandescent lamp and the electronic flash passes. The illumination is focused on the patient's cornea by means of an adjustable mirror arrangement in the tube (3 in Fig. 2). The activating blue interference filter is inserted in the vertical part of the T tube.

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In principle the arrangement used consists of two synchronized automatic cameras with a common electronic flash. Each of the two recording cameras (Robot Motor Recondor 36 BL) is mounted on an adjustable sliding plate on a wooden platform fixed to the mobile underframe of the Zeiss photo slit lamp.

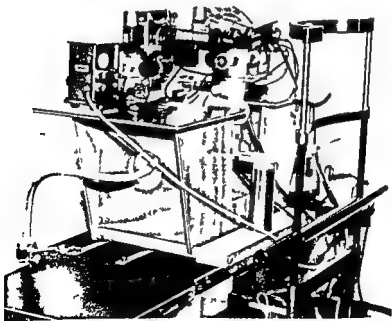


Fig 1

Synchronized cameras for simultaneous fluorescein angiography of both irides

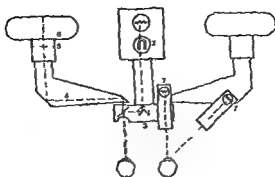


Fig. 9

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|---|---|
| 1 Incandescent lamp illumination | 5 Secondary filter |
| 2 Electronic flash tube | 6 Robot motor camera |
| 3 Light distribution tube with primary filter | 7 Focusing lamps (shown on the right side only) |
| 4 Right angled objective tube | |

Diagram showing the paths of light rays for the adjustment of the cameras by incandescent lamp illumination (1-3) for electronic flash illumination of the irides (2-3) for photography (4-6) and for the focusing lamps (7-7)

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Each camera is provided with a device for optical registration of the time and exposure number - reflected from a timepiece and film counter built into the desk and of previously recorded patient data. A green yellow secondary filter is inserted in the holder of each camera.

The generator used for retinal angiography supplies current across a foot operated switch to the two cameras the incandescent lamp and the electronic

flash and at the same time the current controls the complex interaction between the magnetic shutters the film feed mechanism and the electronic tube discharges in step with the pre set exposure rate. In order to spare the electron tube during the many exposures at short intervals it is cooled by an air current from a vacuum cleaner otherwise some flashes may drop out at full current intensity.

The distance from the patient's eyes to the objectives is a little more than 90 mm and with stop 11 the definition of depth is approx 5 mm. As the Robot cameras are not of the reflex type for focusing at varying object distances it is necessary to use a fixed object distance determined by means of two small focusing lamps placed beside each other and screwed on to each of the rotatable objectives. One of the lamps is placed in the sagittal plane and depicts a bright vertical line on the patient's cornea while the other stands at a horizontal angle of 45° and shows a lying cross. By means of the sliding plates the positions of the cameras are adjusted until the vertical line falls in the point of intersection of the two bars of the cross in the cornea of each eye. Both cameras are then at the correct distance which may be checked by removing the backs of the cameras and replacing them by ground glass screens for focusing.

Films Kodak Tri-X 24 × 36 mm ASA 400 DIN 27

Primary filter Blue interference filter No 137 (max transmission 420 nm) calculated and produced by Werner Olsen Head of the Optical Laboratory the Academy for Technical Sciences 2800 Lyngby Denmark

Secondary filter Green yellow Schoot GC 14/3 mm (515–530 nm)

Fluorescein sodium solution 3 ml 20% injected into a cubital vein

Generator Intensity IV (840 watt sec)

Exposure interval 1.2 or 1.5 sec

Photo objectives Stop 11

Negative enlargement 1.5 ×

On the negatives the passage of the fluorescein containing blood can easily be followed especially in light irides. In the first phase filling of the arteries is first seen in a small area at the iris root continuing towards the pupillary margin. The second phase reveals the characteristic loops of the iris vessels at the pupillary margin. During the third phase filling of the iris vein occurs. The fluorescent vascular loops can be used for time marking while the incipient arterial fluorescence at the iris root is too scattered and indistinct to be used as a definite criterion.

The fluorescent vascular loops at the pupillary margin present in the negatives as a number of dark dots along the narrow light zone which represents the pigmented pupillary seam. The veins are visualized about 2 seconds later in their peripheral course they are less tortuous than the arteries.

According to Baggesen (1969) the circulation times in fluorescein angiography of the iris are as follows

	Average sec	Range sec
Arm to iris	15.4	9.0-22.5
Iris root pupillary margin	2.6	0 - 6.0
Iris arteries iris veins	5.9	4.5- 7.5

In simultaneous angiography of the irides of normal eyes the fluorescent dots at the pupillary margin appear at the same time in the two eyes. In doubtful cases the maximum time difference is 1.2 sec which corresponds to the time interval at the exposure rate used.

In order to test the reliability of the method four patients with stenosis of the internal carotid artery which had been confirmed by arteriography were subjected to simultaneous fluorescein angiography of the irides.

Case 0610/9 A man aged 45 with acute right sided hemiparesis. Arteriography had disclosed severe stenosis of the left internal carotid artery just above its origin. The stenosis was only about 2 mm in length, lumen 2 mm in diameter.

Case 141/18 A man aged 53 with right sided hemiparesis of 3 years duration. Arteriography had revealed occlusion of the left internal carotid artery high on the neck. Repeat arteriography in relation to fluorescein angiography of the irides was unsuccessful on both sides.

Case 1607/93 A man aged 44 who had suffered from petit mal seizures for a couple of years, suddenly followed by a grand mal seizure. Left sided arteriography had shown stenosis of the internal carotid artery 1 cm in length, about 3 cm from the bifurcation.

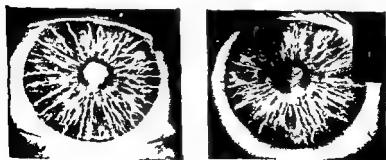


Fig. 3

Fluorescein angiography of the irides in a patient with occlusion of the left internal carotid artery (Case 141/18)



Fig 4

Fluorescein angiography of the irides in a patient with stenosis of the left internal carotid artery (Case 160224)

Case 311009 A man aged 63 with acute right sided hemiparesis. Arteriography had revealed a very distinct narrowing at the origin of the internal carotid artery. The lumen was apparently 2-3 mm in diameter.

In all four patients the fluorescein exposures showed diminished and delayed filling of the iris vessels on the side of the stenosis as seen in Figs 3 and 4.

On the assumption that digital compression of the common carotid artery in normal individuals would result in a similar distribution of the fluorescein



Fig 5

Fluorescein angiography of the irides in a 50 year old man 15 seconds after digital compression of the right common carotid artery

in the irides angiography was performed on a 50 year old colleague who offered to volunteer. The result was surprising: distinct and early filling of the iris vessels on the compressed side but diminished and delayed filling on the opposite side (Fig. 5).

Fluorescein angiography was then performed on some medical students. In each experiment digital compression of the common carotid artery done by the same experienced neuroradiologist resulted in diminished blood flow in the iris vessels on the opposite side.

The observation of contralateral delayed and diminished iris fluorescence on digital compression of the common carotid artery is in agreement with the phenomenon reported by Høedt Rasmussen & Skinhøj (1964) viz diminished blood flow in the opposite unaffected hemisphere on carotid compression in patients with apoplexy which they termed transneural depression. Similar observations have been reported by Borrás et al. (1969) during pressure measurements in the supra-orbital artery and by Solis et al. (1972) in the recording of spontaneous bulbar pulse amplitudes.

Slit lamp observations of delicate vessels in the contralateral iris confirm the above mentioned results of fluorescein angiography: narrowing of the vessels occurs a couple of seconds after the commencement of compression of the carotid artery.

Acknowledgement

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**OXYPHENBUTAZONUM (TANDERIL®) AS AN ADJUVANT
IN TREATMENT OF DENDRITIC KERATITIS**

**Double Blind Trial Using
Fluorescein Rose Bengal Vital Staining**

BY

M S NORN

A prospective study based on double blind trials of 29 fresh cases of dendritic keratitis revealed failing effect of oxyphenbutazonum (NFN). Vital staining with fluorescein rose bengal showed three phases I The proper dendritic pattern lasting on an average five days II A collection of vital stained dots grouped over the area of the previous pattern present for about another 7-14 days This was followed by phase III a few dots often scattered diffusely over the whole cornea present for another 9-11 days on the average In most cases the rose bengal staining persisted the longest Geographic ulcer developed in five cases The duration of iduri d no treatment is discussed

Key words: keratitis - dendritic - herpetic - oxyphenbutazonum - Tanderil® - vital staining - fluorescein - rose bengal

Steroid treatment is well known to be contraindicated in dendritic keratitis at least in the initial phase (Thygeson)

Oxyphenbutazonum (NFN) (Tanderil®) is an anti inflammatory drug It

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has an improving effect on oedema and hyperaemia presumably owing to an influence on the vessels. In herpes cell cultures and in rabbit experiments with virus inoculated on the cornea (Goetz Jones) Tanderil has been shown at least not to stimulate the growth of herpes virus.

Herpetic keratitis is still difficult to treat. New therapeutic possibilities should be considered and evaluated (Graupner et al, Pivan Langston et al). I accordingly decided to try Tanderil instead of steroids starting with a series in which the active phase of dendritic keratitis was over.

In this former study I showed that Tanderil ointment is tolerated by patients having previously had a pronounced dendritic keratitis. A total of 17 patients were given Tanderil ointment. In three of these slight punctate staining was seen following the treatment while in four previous slight punctate staining persisted unchanged. In the remaining ten staining was seen neither before nor after the treatment. Cicatrices and visual acuity remained unchanged. No relapses occurred during the Tanderil treatment (Norn 1970a).

It is perhaps not surprising that Tanderil has no effect in the inactive phase. Still it may be worthwhile investigating whether Tanderil can abate the acute herpes infection. We do not know the mechanism of the anti-inflammatory effect of Tanderil. An oedema-reducing action may have a favourable influence at the acute stage of the disease. It may perhaps shorten this stage and prevent or reduce such complications as might follow it.

Inspired by Geigy's Ophthalmology Workshop at Kandersteg, Switzerland, January 1970, I have since carried through a double-blind trial of patients with fresh dendritic keratitis treated with Tanderil or placebo.

The patients were also treated with IDU (5-iodo-2'-deoxyuridine). IDU has been proven to shorten the individual dendritic keratitis attack. I showed in a previous study that unfortunately IDU does not reduce the recurrence rate. On the contrary, I noticed a greater number of relapses which however were of shorter duration and probably less dangerous (Norn 1970b).

Material

A series of 29 patients suffering from typical acute untreated dendritic keratitis were collected during three years, partly from the Out-Patient Ophthalmic Department, *Kommunehospitalet*, and partly from my own practice at Vanløse. The diagnosis was based on the typical dendritic pattern. Virus culture was not performed.

Method

The cornea was examined by vital staining with a mixture of fluorescein and rose bengal (50 mg fluorescein 50 mg rose bengal 45 mg sodium chloride distilled water to 5 ml Norn 1972). The vital staining was charted green indicating fluorescein staining and red rose bengal staining.

The patient was subjected initially to the following treatment 1% IDU eye drops hourly during all waking hours i.e. about 16 times a day 2% IDU eye ointment at night 10% Tanderil eye ointment 6 times a day.

The patient was seen for control two or three days later. Vital staining was performed and the result again charted. The control continued in the same manner at these intervals for 3-4 weeks and then at somewhat longer intervals for practical reasons.

In case of improvement the treatment was scaled down to IDU drops 6 times daily IDU ointment at night Tanderil eye ointment 6 times daily. In case of further improvement scaling down to IDU drops 3 times daily IDU ointment at night Tanderil eye ointment 3 times daily (cf Fig. 1).

The treatment was discontinued when the cornea was no longer stained or if pronounced exacerbation was noticed contraindicating continued treatment (development of geographic ulcer or exacerbation after treatment for more than one month). In these cases cauterisation with iodine was performed and terramycin with polymyxin ointment was given.

Tanderil Effect?

The Tanderil ointment contains 10% oxyphenbutazone in a soft diffuent ointment base (petroleum jelly paraffin and lanolin).

The tubes had been delivered by the firm Geigy Switzerland. Each tube was provided with a code number (1-30). The code was broken after the recording of the results on April 11 1973 by the author and Geigy's representative (G.F.) jointly. The following 15 tubes were then seen to have contained Tanderil nos 1 5 6 7 9 10 13 15 16 20 22 24 25 26 and 27. The remaining 14 tubes of identical appearance contained no Tanderil.

The result arrived at was that Tanderil was shown to have no other effect than the placebo. No statistically significant difference was demonstrated between the Tanderil and placebo treated patients (Table I).

The following parameters were studied. Number of days with continued presence of a dendritic pattern. Number of days with accumulated fluorescein

Table I
Number of patients on Tanderil or placebo treatment Periods I-III of Fig 1
(fluorescein staining)

	Total	≤ 5th day	> 5th day	≤ 1th day	> 1th day
Period I					
Tanderil	15	7	8	11	4
Placebo	14	10	4	13	1
	Total	≤ 7th day	> 1th day	≤ 20th day	> 20th day
Period II					
Tanderil	15	5	10	9	6
Placebo	14	6	8	11	3
	Total	≤ 7th day	> 7th day	≤ 30th day	> 30th day
Period III					
Tanderil	15	4	11	9	6
Placebo	14	6	8	11	3

stained dots and correspondingly with accumulated rose bengal vital stained dots. Number of days with scattered fluorescein dots left and correspondingly with rose bengal dots left. The periods were reckoned from the first day the patient was subjected to treatment (Fig 1).

Further the first day was recorded on which the vital staining was noted to have definitely ceased and finally the numbers of days of maximum therapy of treatment 6 times a day 3 times a day and the total period of treatment.

Geographic ulcer developed in four Tanderil treated patients and in one placebo-treated patient.

The mean age of the Tanderil group was 54 and that of the placebo group 50. There was no sex difference between the two groups (nine males and six females in the Tanderil group eight males and six females in the placebo group).

The Tanderil series had the disadvantage of including two patients suffering

in advance from a *metaherpetic* disciform keratitis. The placebo group contained no such cases.

The incidence of previous dendritic keratitis was not higher in the Tanderil group than in the placebo group (six relapses in the former and seven in the latter).

No instances were observed of allergy caused by Tanderil or ointment base nor any cases of aggravated dendritic pattern or fresh dendritic pattern. None developed metaherpetic complication, secondary glaucoma or iritis.

Summary: we may conclude that the Tanderil ointment had neither a favourable nor a harmful effect on the fresh dendritic keratitis attack.

Vital Staining Phases

Fig 1 illustrates diagrammatically the courses of the 29 fresh dendritic keratitis cases vital stained with a mixture of 1% fluorescein and 1% rose bengal.

The first five days a typical dendriform pattern was seen. The branch itself was red stained by rose bengal and outlined by a green fluorescent double contour. The red region represented the diseased epithelial cells. The green fluorescein dye penetrated through defects of the epithelial layer and spread from this within the intercellular spaces in between neighbouring cells and more deeply in some instances as far as the aqueous humour. The red stained dendriform pattern represented virus affected epithelial cells while the green double contour disclosed presence of epithelial defects as well.

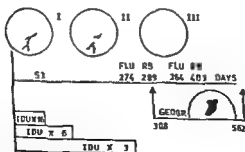


Fig 1

Course and vital staining in 29 patients with fresh dendritic keratitis. The figures indicate days after instituted treatment. Five patients developed geographic ulcer. FLU means fluorescein and RB rose bengal vital staining.

After on an average five days only uncharacteristic remains were left of the previous dendritic pattern in the form of accumulated vital stained dots localized within parts of the previous pattern. Some such remains were fluorescein stained epithelial defects and others rose bengal stained degenerate epithelial cells. The rose bengal stained persisted the longest on an average 28.9 days against the fluorescein stained 27.4 days after the start of the treatment.

This second phase was followed by a third one during which punctate fluorescein and/or rose bengal staining might still be seen but now only represented by a few dots as a rule scattered over the whole cornea also outside the original dendritic pattern. The rose bengal staining lasted the longest 40.3 days (fluorescein 36.4 days) after treatment had been instituted.

In five cases the condition exacerbated with development of a superficial irregularly outlined so called geographic ulcer. This ulcer occurred from 10 to 68 days after the disease had been diagnosed and subsided from 20 to 91 days after the diagnosis.

The geographic ulcer was stained intensely red and had a pronounced fluorescent outline. In other words the bottom consisted of degenerate cells with defects.

On examining the 29 cornea the last time staining was noticed both fluorescein and rose bengal stained dots were found in 12 cases rose bengal stained alone in 14 and fluorescein stained alone in 3.

These findings evidenced the justification of using the vital stain mixture important information being missed by using fluorescein for instance alone!

Discussion

In the small series under review Tanderil was found to have no other effect on dendritic keratitis than placebo. Tanderil was employed six times daily at most in the form of a 10% ointment. More intense treatment (20% hourly) or a different way of administration (general) might possibly lead to another and perhaps more favourable result.

The anti-inflammatory effect of Tanderil has been established in various diseases. The failing response noticed in this series may be accounted for by the absence of vessels in the cornea the point of attack of Tanderil being in fact the vascular wall.

Vital staining with a mixture of fluorescein and rose bengal showed the importance of using both components.

The vital staining disclosed that the cornea does not calm down till long

after the dendritic pattern has subsided. The dendriform phase is succeeded by one with a group of vital stained dots. This is subsequently succeeded by a phase with fewer dots scattered diffusely over the whole cornea.

Use of rose bengal seems to be particularly important when one desires to make out whether pathological corneal epithelial cells are still present.

At a follow up of 107 patients previously attacked by dendritic keratitis (Norn 1970c) I found that vital staining was still visible in 35 per cent. Two even had relapses at the time of the follow up. Five displayed grouped staining, eight pronounced fluorescein and rose bengal staining, three considerable rose bengal staining and the remaining slight punctate staining. In addition I noticed that 81 per cent had a reduced corneal sensitivity and 79 per cent defects of Fischer-Schweitzer's fluorescein pattern (Norn 1970d).

These observations showed the cornea to be abnormal after an attack of dendritic keratitis. The herpes virus may disappear but the cornea will remain in an inferior condition. Even in cases where detailed vital staining shows stainable regions to be no longer present we must expect appearance of fresh vital staining weeks or months later in a small number of cases due to a proper recurrence of dendritic keratitis and in others merely in the form of punctate staining.

How are the grouped punctate staining (phase II) and the diffuse punctate staining (phase III) to be interpreted? The diffuse staining is seen at a time when the IDU treatment often has been discontinued without recurrence having been noticed. There is reason to suppose that the herpes virus has disappeared or become inactive and that we are faced with an inferior perhaps hyposen- sitive neurotrophic cornea with no active virus infection. Phase II will at least in its latter part likewise be without any active virus.

The IDU treatment has its advantages and its disadvantages. At the active stage of dendritic keratitis it kills the virus being therefore indicated. When the virus is inactive IDU is not indicated having a cytotoxic effect on the restoring phase of the corneal epithelium. IDU may be suspected to prolong phase II and in particular phase III and to interfere with the healing of a geographic ulcer.

In the present series we continued the IDU treatment as long as possible together with the Tanderil treatment. Fig. 1 shows that the IDU treatment was continued until the end of phase II (after on an average 23.6 days). The IDU treatment should probably be discontinued much earlier e.g. by the time the dendritic pattern has subsided and localized punctate residual staining is on the decline (about the middle of phase II). In cases of a failing IDU effect it may be appropriate to change to a different treatment as early as after one week for fear of IDU resistant herpes virus (iodine cauterisation, adenine arabinoside).

Acknowledgements

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THE MORPHOLOGY OF THE SHEEP RETINA

I The receptor cells and the pigment epithelium

BY

SVEN ERIK G. NILSSON BENGT G. KNAVE HANS E. PERSSON
and TÖNIS LUNT

The present investigation was undertaken in order to provide a necessary ultrastructural basis for the complete interpretation of recent findings on the electrophysiology of the sheep retina and on the influence on retinal function of certain drugs and toxic substances. The sheep retina was shown to be a mixed retina with a rather large number of cones. The receptor cells were conventional in shape. Typical differences in light and electron optical density between rod and cone ellipsoids could be explained as differences in stainability of the mitochondrial content. Specific connections between the outer segment disks and the plasma membrane as well as the occurrence of phagosomes in the pigment epithelial cells are discussed in relation to the development and the renewal of the receptor outer segment. No melanin granules were seen in the pigment epithelium of the investigated specimens which were all taken from the tapetal area of the fundus. The possible relation between lipid like bodies in the pigment epithelium and vitamin A metabolism is discussed.

Key words: retina — receptor cells — pigment epithelium — electron microscopy — sheep

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In a recently published investigation the sheep electroretinogram (ERG) was studied (Knave et al 1972). By using subliminal iterative light stimuli the ERG was analysed below its conventional threshold i.e. the b wave threshold which led to a re interpretation of the major components of the ERG. Besides the rod and cone receptor potentials the results indicated positive and negative d.c. responses from the inner nuclear layer and a late slow positive response corresponding to the conventional c wave at higher stimulus intensities.

Furthermore the sheep was chosen as experimental animal when studying differential effects on retinal functions of some neuro pharmacologically active substances and drugs (Bernhardt et al 1973, Knave et al 1973a, Knave et al 1973b).

In contrast to the extensive knowledge of the function of the sheep retina very little information is available about its morphology. An electron microscopic study on the sheep pigment epithelium has been published (Leure DuPree (1968)) but so far no systematic ultrastructural analysis of the retina.

Therefore the aim of the present investigation is to describe the main morphological features of the sheep retina as a necessary basis for the complete interpretation of the general electrophysiological findings as well as of the effects of toxic substances and drugs on retinal function.

Material and Methods

Eyes from light adapted domestic sheep were fixed by perfusion with 1% glutaraldehyde in 0.1 M cacodylate buffer via the common carotid artery. The perfusion pressure was kept well above the arterial blood pressure. Following perfusion the eye was enucleated and the anterior segment cut away. When opening the eye a rather large green reflecting band was seen in the posterior part of the fundus. This band corresponds to a tapetum lucidum in the choroid. Fixation was then continued by means of immersion in the same fixative. After a few days the eye was cut in smaller pieces. The sclera and most of the choroid were dissected away from each piece. At this stage the dissection could be performed without causing at the same time detachment of the retina. Postfixation was carried out in 1% osmium tetroxide in the same buffer. After dehydration in acetone the specimens were embedded in Vestopal W. Pieces of retina and the pigment epithelium from the tapetal area of the fundus, not far from the posterior pole of the eye, were cut for light and electron microscopy. No systematic search for the area centralis was made. The ultrathin sections were examined in a Philips 300 electron microscope.



Fig 1

light mic ograph of sheep retina Re receptor cells OP outer plexiform layer IN inner nuclear layer II inner plexiform layer G ganglion cells Ax axons Empty capillaries are seen from the axonal layer to the outer plexiform layer 1109

Observations

The pigment epithelium and the retina with all its well known layers are shown in a survey light micrograph (Fig 1) The number of rods considerably exceeded that of cones Yet the number of cones was rather large The total length of the rods and cones was about 50μ and 40μ respectively

Rod as well as cone outer segments were quite conventional in shape (Fig 3) A rod outer segment was about 13μ in length and 1.8μ in diameter (Fig 2) A cone outer segment was only about 4μ in length (Fig 3) Its diameter at the base slightly exceeded that of a rod Whereas rod outer and inner segments were approximately equal in length and in diameter the cone inner segment measured about 8μ in length and 2.5μ in diameter

The rod outer segment consisted of an average of about 650 double membrane disks (Figs 2 and 4) The two membrane elements of each disk were closely packed (Fig 5) As to the majority of the disks no continuities with the plasma membrane were seen Only at the base of the rod outer segment a few disks were continuous with the plasma membrane (Fig 5) The cone outer segment contained rather few disks about 150 (Figs 3 and 6)

In the pictures the cone disks were very frequently seen to be continuous with the plasma membrane not only at the base but also over the entire length of the outer segment (Fig 6) The two membrane elements of each disk were separated by an interspace Thin inner segment processes were observed along the basal part of the outer segment of rods as well as of cones (Fig 2) A so called connecting structure linked the outer segment to the inner segment (Fig 4)

The marked difference in optical density between rods and cones seen already in a light micrograph (Fig 1) could be shown in the electron micrograph (Fig 3) to be due to a striking difference between the mitochondria of rod and cone ellipsoids Whereas in the rod mitochondria the spaces between the cristae were only lightly stained and of about the same electron density as the cytoplasmic ground substance (Fig 4) the spaces between the cristae of the cone mitochondria were filled with a much more electron dense material (Fig 6) The concentration of mitochondria was greater in cones than in rods

In the myoid (Fig 3) which is located adjacent to the ellipsoid ribosomes and a Golgi apparatus were seen In this respect rods and cones were qualitatively similar to each other

The cone nuclei were located in the most peripheral row of the outer nuclear layer (Fig 3) They were slightly less electron dense than the rod nuclei

The receptor nuclei fibers and synaptic bodies (which will be described in the following paper) were surrounded by thin layers of the lightly stained



Fig

Rod outer (RO) and inner (RI) segments. A pigment epithelial cell (P) is seen at the top of the figure. 9,500



Fig. 3

Rods (R) and cones (C) O outer segment I inner segment E ellipsoid M myoid
N nucleus Mu Muller cell Arrows indicate attachment zones corresponding to the
outer limiting membrane $\times 8\ 00$

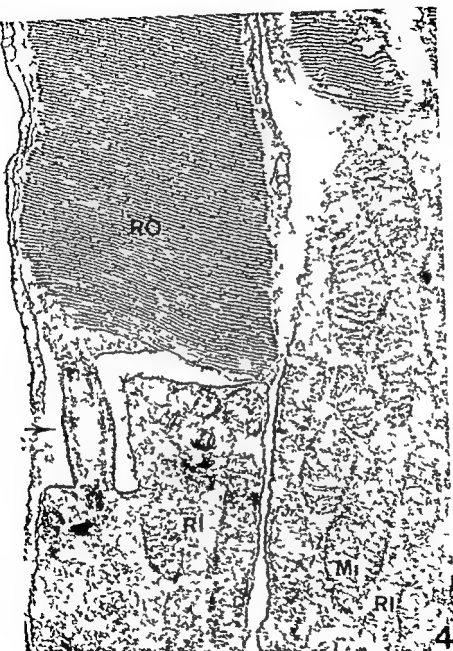


Fig 4

Rod outer (RO) and inner (RI) segments. Arrow indicates the connectin structure. The mitochondria (Mi) are lightly stained. 44 000



Fig 3

Rods (P) and cones (C) O outer segment I inner segment L ellipsoid M myoid
N nucleus Mu Müller cell Arrows indicate attachment zones corresponding to the
outer limiting membrane $\times 8,00$

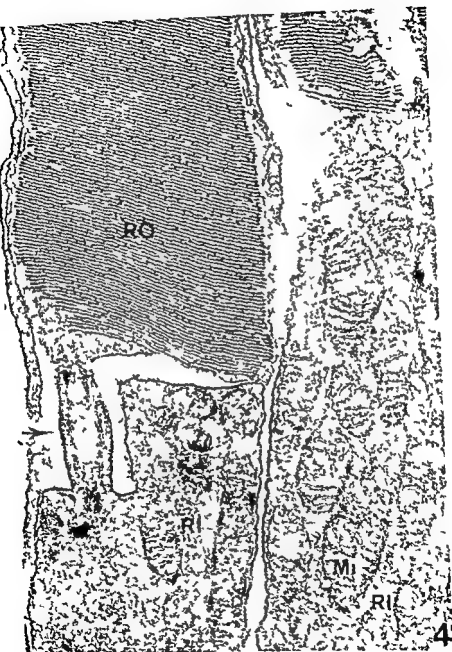


Fig. 4

Rod outer (RO) and inner (RI) segments. Arrow indicates the connecting structure. The mitochondria (MI) are lightly stained $\times 44\,000$

Muller cells Attachment zones between the Muller cells and the receptor cells corresponding to the so called "outer limiting membrane" were located just sclerally to the cone nuclei (Fig 3) Thin Muller cell processes also extended somewhat farther sclerally between the inner segments Thus the receptor cells were separated from each other by Muller cells from the inner segments to the outer plexiform layer

A well preserved relationship between the pigment epithelium and the receptor outer segment is demonstrated in Figs 2 and 7 Pigment epithelial processes surrounded the tips of the receptor outer segments (Figs 2 and 7) Adjacent to

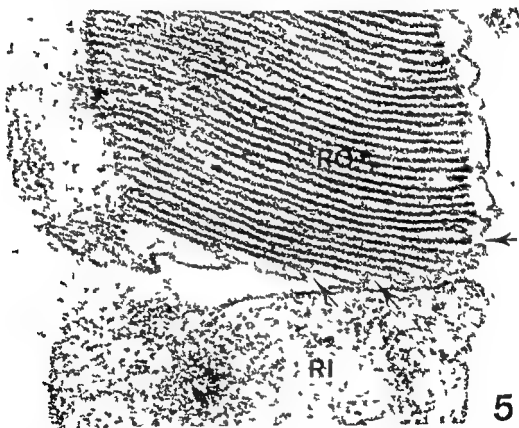


Fig 5

In a sheep rod the disks are seen to be continuous with the plasma membrane only at the base of the outer segment (arrows) $\times 10,000$

Fig 6

In a sheep cone the disks are seen to be continuous with each other and with the plasma membrane along the lateral surface of the outer segment (arrows) The mitochondria (Mi) are quite electron dense as compared to those of a rod (Fig 4) $\times 55,000$



Fig 6

Muller cells Attachment zones between the Muller cells and the receptor cells corresponding to the so called "outer limiting membrane" were located just sclerally to the cone nuclei (Fig 3) Thin Muller cell processes also extended somewhat farther sclerally between the inner segments Thus the receptor cells were separated from each other by Muller cells from the inner segments to the outer plexiform layer

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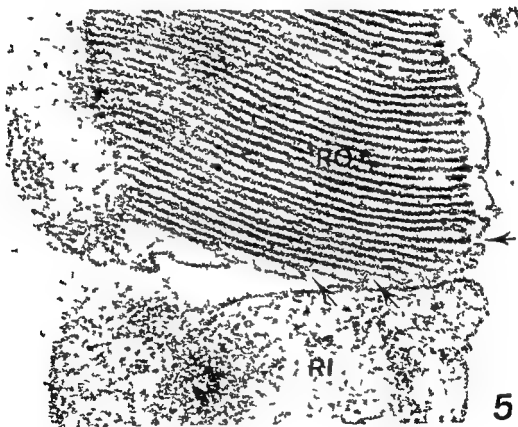


Fig 5

In a sheep rod the disks are seen to be continuous with the plasma membrane only at the base of the outer segment (arrows) $\times 10,000$

Fig 6

In a sheep cone the disks are seen to be continuous with each other and with the plasma membrane along the lateral surface of the outer segment (arrows) The mitochondria (Mi) are quite electron dense as compared to those of a rod (Fig 4) $\times 85,000$

these processes the cytoplasm of the pigment epithelial cell contained at least two kinds of prominent structures the rounded light grey bodies (L) which as judged by appearance may consist of lipids and the bigger and more electron dense phagosomes (Ph) often seen to contain concentrically arranged membranes (Fig 7) The main part of the cytoplasm was occupied by tubular material ribosomes and other particulate material and by mitochondria

The pigment epithelium in this area of the fundus lacked melanine granules however At the choroidal side the plasma membrane of the pigment epithelial cell showed fairly large infoldings often seen after perfusion fixation The basement membrane (Bruch's membrane) between the endothelial cells of the choroid and the pigment epithelial cells is seen at the top of the figure

Discussion

The retina of the domestic sheep is a mixed retina with a rather large number of cones This finding fits well with electroretinographic observations made by Knave et al (1972)

The striking difference in stainability between rod and cone mitochondria reflects a difference in chemical reaction properties which may be of significance also with respect to the normal metabolism

Between the species a varying relative location of the rod and cone nuclei is seen In sheep as in human the cone nuclei are located in the most peripheral row of the outer nuclear layer The opposite is true for the frog

Whereas in the sheep rods the two membrane elements of each outer segment disk were closely packed they were separated by an interspace in the cones This difference may be related to the method of fixation to the state of adaptation of the receptor or to the species

In the sheep cones the majority of the outer segment disks were seen to be continuous with the plasma membrane This is in accordance with earlier findings on cones of perch (Sjostrand (1959 1961)) and on cones of frog (Moody & Robertsson (1960) Nilsson (1965)) In the sheep rods however such continuities were observed only for a few disks at the base of the outer segment

Fig 7

Pigment epithelial cell (P) containing phagosomes (Ph) and lipid like bodies (L) but lacking melanin granules The relation between the pigment epithelium and the receptor layer is well preserved The tips of the rod outer segments (RO) are surrounded by pigment epithelial processes BM: basement membrane $\times 18\,000$



Fig

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The same thing was true for frog rods (Moody & Robertsson (1960) Nilsson (1965)) As will be discussed below these basally located continuities are related to the development and the renewal of the receptor outer segment Nilsson (1964) showed that the disks in the young tadpole developed as invaginations of the plasma membrane at the base of the outer segment Since such invaginations were seen also at the basal surface of adult rod and cone outer segments Nilsson (1964) proposed that a formation of new disks is also proceeding at a slow rate in the adult outer segment

This idea was later proven to be correct in beautiful studies by Young (1964) and by Young & Droz (1968) By using labelled amino acids they could show that the rod receptor outer segment was continuously renewed from the base The turnover time was 9-10 days for mouse and rat and about 6 weeks for frog It seems quite clear that the same principle is valid also for the sheep

The large membrane containing bodies the phagosomes observed in the pigment epithelium of the sheep are also closely related to the turnover of the receptor outer segment This fact was shown by Young & Bok (1969) The tips of frog rod outer segments were seen to be repeatedly incorporated into the pigment epithelium In the phagosomes the membrane material became chemically changed It was finally eliminated from the cell Certain hereditary retinal degenerations may be explained by a defect of this phagocytosis (Bok & Hall (1969) Herron et al (1969))

Lipid like bodies (L) were also seen in the sheep pigment epithelium In the frog, these bodies were shown to concentrate vitamin A taken up from the circulation (Young & Bok (1970)) Vitamin A is the well known precursor of retinal It is obvious that the pigment epithelial cell is a very important metabolic barrier between the circulation and the receptor cells The metabolic exchange between the pigment epithelium and the receptor outer segments may be aided by the pigment epithelial processes

Whereas Leure DuPree (1964) described melanin granules in the sheep pigment epithelium no such granules were found in the present study This discrepancy is probably explained by the fact that the material used in this investigation was taken from the tapetal area of the fundus which is known to lack these pigment granules

Ultrastructural as well as electrophysiological studies on the effect of toxic substances on the pigment epithelium are in progress (Anzic et al 1973a b)

The receptor synaptic bodies and the remaining layers of the retina will be described in a following paper

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THE MORPHOLOGY OF THE SHEEP RETINA

II The inner nuclear layer the ganglion cells and the plexiform layers

BY

SVEN ERIK G NILSSON BENGT G KNAVE TÖNIS LUNT
and HANS E PERSSON

The aim of the present study was to provide an ultrastructural basis necessary for the full understanding of recent electoretinographic observations on normal sheep and on sheep where the retinal function was influenced by certain drugs and toxic substances. The ultrastructure of the inner nuclear layer, the ganglion cell layer and the plexiform layers of the sheep retina is described. The horizontal cells were rather few and only one type was observed. Two types of bipolar cells were found. The number of amacrine cells was quite large, indicating well developed lateral connections in the inner plexiform layer. Few ganglion cells were seen. The synaptic contacts between the receptor cells, the horizontal cells and the bipolar cells as well as the synaptic contacts between the bipolar cells, the ganglion cells and the amacrine cells are discussed in relation to findings on other species.

Key words: retina - inner nuclear layer - ganglion cell layer - plexiform layers - electron microscopy - sheep

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As was mentioned in a preceding paper on the ultrastructure of the receptor cells and the pigment epithelium of the sheep retina (Nilsson et al 1973) a large amount of new electrophysiological data relevant for the interpretation of the components of the ERG and of interest for a further development of the clinical ERG (Knave & Nilsson 1973) has been obtained by Knave et al in experimental work on the sheep (Bernhard et al 1973 Knave et al 1972 Knave et al 1973 a b). In order to make it possible to correlate structure and function under normal conditions as well as after the influence on the retina of toxic substances and drugs the present ultrastructural investigation of the sheep retina was undertaken.

Material and Methods

Eyes from light adapted domestic sheep were fixed by perfusion with 1% glutaraldehyde postfixed in 1% osmium tetroxide dehydrated in acetone and embedded in Vestopal W. Pieces of retina from the tapetal area of the fundus not far from the posterior pole of the eye were studied in light and electron microscopy (Philips 300). For further details see Nilsson et al (1973).

Observations

A cone pedicle and some rod spherules are demonstrated in Fig. 1. Several synaptic structures are present within the wide cone pedicle whereas only one synaptic apparatus is seen in the smaller rod spherule. Muller cell (glial) processes separate the synaptic bodies. Interreceptor contacts by means of small processes were observed occasionally. In the center of Fig. 2 a synaptic apparatus of a rod spherule is shown. It consists of a synaptic ribbon (generally accepted as an indication of a synaptic contact) on top of two lateral elements and one central element invaginated from the outer plexiform layer. A positive identification of these elements as representing bipolar and/or horizontal cells cannot be made without serial sectioning. Such data are available from some other species and comparisons will be made below. Thickenings along the synaptic body plasma membrane lining the invaginated structures are seen in Fig. 2.

The inner nuclear layer contains the cell bodies of horizontal cells, bipolar cells, amacrine cells and Muller cells. The horizontal cells located in the outermost row of the inner nuclear layer were rather few. Their cell bodies

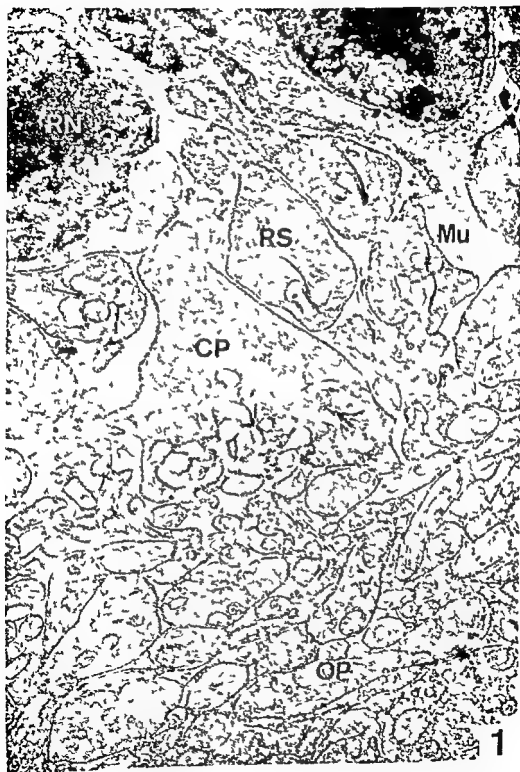


Fig 1

A cone pedicle (CP) and rod spherules (RS) with their synaptic structures are demonstrated IN rod nucleus Mu Muller cell OP outer plexiform layer $\times 15\,000$



Fig 2



Fig 3



Fig. 4



Fig 5

Fig 2

A typical synaptic apparatus of a rod spherule (RS) with a synaptic ribbon on top of two lateral elements and one central element invaginated from the outer plexiform layer $\times 34\,000$

Fig 3

At the border between the outer plexiform layer (OP) and the inner nuclear layer a horizontal cell (H) is seen B bipolar cell Mu Muller cell $\times 7\,600$

Fig 4

Two kinds of bipolar cells (B) are seen those of low electron density and those of moderate electron density Arrows indicate bipolar cell processes H horizontal cell Mu Muller cell C empty capillary $\times 8\,100$

Fig 5

A light and a dark bipolar cell (B) in close relation (arrows) to a horizontal cell process (H) $\times 7\,100$



Fig. 4

were bigger and their processes generally thicker than those of the bipolar cells (Figs 3 and 4). The nuclei often showed indentations. A prominent Golgi apparatus was present (seen to the right of the nucleus in the figures). The main processes of the horizontal cells were seen to run parallel to the outer plexiform layer close to the nuclear layer. Several small branches were found to leave the main process in a scleral direction where they could no longer be followed in single sections.

The bipolar nuclei were rounded in shape (Figs 4 and 5) a distinct difference from the angular Muller cell nuclei which were located at the same level. With respect to electron optical density of the cytoplasm as well as of the nucleus two kinds of bipolar cells a dense one (dark) and a less dense one (light) were observed (Figs 4 and 5). Both kinds were randomly distributed. A nucleolus could be seen in the light type as well as in the dark type. From both types of cell bodies processes could be followed to the outer plexiform layer and to the inner plexiform layer. Two such processes are illustrated in Fig 4 (arrows). Within the inner nuclear layer the bipolar cells were always separated from each other by Muller cells often in the form of very thin sheets. Both

Fig 6

Three Muller cell bodies (Mu) typically angular in the center of the figure. The left one can be followed to the inner plexiform layer (IP) (see also Fig 1 and 8). Two amacrine cells (A) in the lower part of the picture. B bipolar cells $\times 8600$

Fig 7

Lower right part of Fig 6 at higher magnification. A Muller cell process (Mu) is seen between two amacrine cells (A). Arrows point at indentations of the amacrine cell nucleus $\times 16000$

Fig 8

Adjacent section to the one shown in Fig 7. Still higher magnification. The Muller cell sheet (Mu) is seen to envelop several other processes at the border of the inner plexiform layer. A amacrine cells $\times 36000$

Fig 9

Survey picture from the inner plexiform layer. A amacrine cell $\times 18600$

Fig 10

Synaptic contacts in the inner plexiform layer. B presumably a bipolar cell terminal. Arrow synaptic ribbon characteristically positioned opposite two adjacent neuronal processes. Two arrows special zcd contact without a synaptic ribbon $\times 60000$

Fig 11

Synaptic contacts in the inner plexiform layer. B presumably a bipolar cell terminal. One of the adjacent neuronal processes shows a concentration of vesicles (arrow) suggesting a synaptic contact back onto the bipolar terminal $\times 48000$

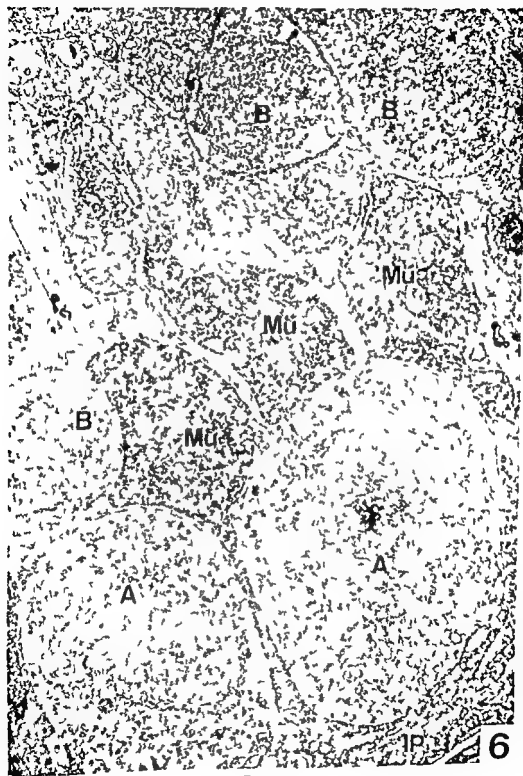


Fig. 1

were bigger and their processes generally thicker than those of the bipolar cells (Figs 3 and 4). The nuclei often showed indentations. A prominent Golgi apparatus was present (seen to the right of the nucleus in the figures). The main processes of the horizontal cells were seen to run parallel to the outer plexiform layer close to the nuclear layer. Several small branches were found to leave the main process in a scleral direction where they could no longer be followed in single sections.

The bipolar nuclei were rounded in shape (Figs 4 and 5) a distinct difference from the angular Muller cell nuclei which were located at the same level. With respect to electron optical density of the cytoplasm as well as of the nucleus two kinds of bipolar cells a dense one (dark) and a less dense one (light) were observed (Figs 4 and 5). Both kinds were randomly distributed. A nucleolus could be seen in the light type as well as in the dark type. From both types of cell bodies processes could be followed to the outer plexiform layer and to the inner plexiform layer. Two such processes are illustrated in Fig. 4 (arrows). Within the inner nuclear layer the bipolar cells were always separated from each other by Muller cells often in the form of very thin sheets. Both

Fig 6

Three Muller cell bodies (Mu) typically angular in the center of the figure. The left one can be followed to the inner plexiform layer (IP) (see also Figs 7 and 8). Two amacrine cells (A) in the lower part of the picture. B bipolar cells $\times 8,600$.

Fig 7

Lower right part of Fig 6 at higher magnification. A Muller cell process (Mu) is seen between two amacrine cells (A). Arrows point at indentations of the amacrine cell nucleus $\times 16,000$.

Fig 8

Adjacent section to the one shown in Fig 7. Still higher magnification. The Muller cell sheet (Mu) is seen to envelop several other processes at the border of the inner plexiform layer. A amacrine cells $\times 36,000$.

Fig 9

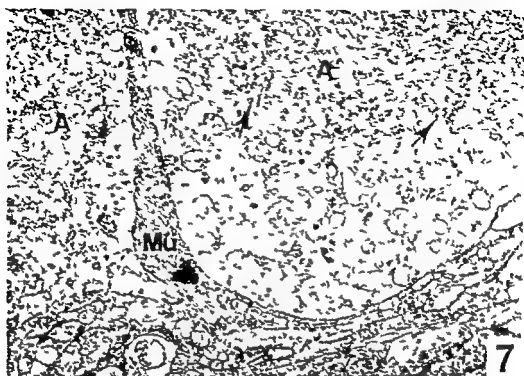
Survey picture from the inner plexiform layer. A amacrine cell $\times 18,600$.

Fig 10

Synaptic contacts in the inner plexiform layer. B presumably a bipolar cell terminal. Arrow synaptic ribbon characteristically positioned opposite two adjacent neuronal processes. Two arrows specialized contact without a synaptic ribbon $\times 60,000$.

Fig 11

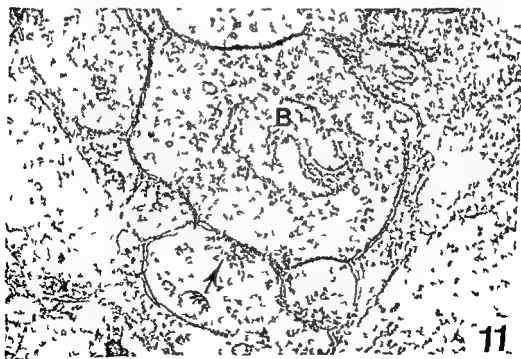
Synaptic contacts in the inner plexiform layer. B presumably a bipolar cell terminal. One of the adjacent neuronal processes shows a concentration of vesicles (arrow) suggesting a synaptic contact back onto the bipolar terminal $\times 48,000$.



Figs 7-8



Fig 9



Figs 10-11

types of bipolar cells were sometimes observed to be in close contact with horizontal cells without Muller cell interposition (Fig. 4 (the dark type) and Fig. 5 (both types)). No tight junctions were found, however. The membrane relations were confirmed at higher magnification.

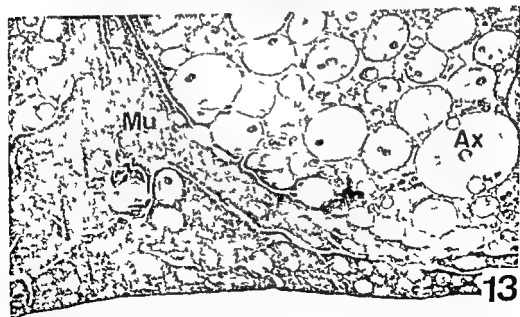
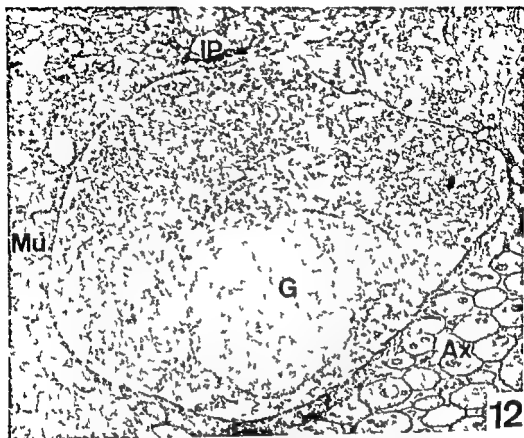
In the innermost row of the inner nuclear layer a rather large number of amacrine cells were seen (Fig. 6). Their cell bodies were bigger than those of bipolar cells. In electron density they showed similarities to the horizontal cells and the light type of bipolar cells. The amacrine cell nucleus always was indented (Fig. 4). In single sections amacrine cell processes could be followed only a minor distance into the inner plexiform layer.

The Muller cell bodies were located in the middle of the inner nuclear layer. They were always angular in shape, filling the spaces between the rounded bipolar and amacrine cells (Figs. 4 and 6). One of the Muller cells in Fig. 6 was followed to the inner plexiform layer for positive identification. In Figs. 7 and 8 it is seen to surround several other processes.

Most of the processes of the inner plexiform layer (Fig. 9) cannot be identified without extensive serial sectioning. For some other species it has been shown, however, that within this layer of the retina synaptic ribbons could be found only in bipolar cell terminals. It seems highly probable that the processes labelled B in Figs. 10 and 11 are bipolar terminals. They contain synaptic ribbons, synaptic vesicles and mitochondria. The synaptic ribbon, which is generally considered to indicate a site of synaptic contact, is characteristically positioned opposite two adjacent neuronal processes (Figs. 10 and 11). Sometimes these two processes appear similar in content (Fig. 10), sometimes different. Whether they are ganglion cell dendrites, amacrine cell processes or one of each kind cannot be determined at this stage. In some cases the localization of vesicles suggests a synaptic contact back onto the bipolar terminal (Fig. 11, arrow). A specialized contact without a synaptic ribbon is demonstrated in Fig. 10 (two arrows).

The ganglion cells were rather few (See also Fig. 1 in the preceding paper (Nilsson et al. 1973)). Their cytoplasm contained a large amount of rough surfaced endoplasmic reticulum and free ribosomes (Fig. 12). Occasionally cells similar in appearance to the ganglion cells were found in the middle of the inner plexiform layer, presumably displaced ganglion cells.

The diameter of the processes of the axonal layer varied a great deal (Fig. 13). The axons were separated from the vitreous by the foot processes of the Muller cells.



Figs 12-13

Discussion

Interreceptor contacts by means of processes were first observed by Sjostrand (1958) (guinea pig retina). He interpreted these contacts as a possible morphological basis for a contrast enhancing lateral inhibition (Sjostrand 1958 1969). Direct membrane relationship over large areas between synaptic bodies were demonstrated by Nilsson (1964) for the frog retina. Interreceptor contacts have also been described for other species such as grey squirrel (Cohen 1964) and human (Missotten 1965 and Cohen 1965). In the sheep retina interreceptor contacts in the form of small processes were observed only occasionally.

The synaptic ribbon positioned in close relation to the lateral elements of the synaptic apparatus is generally accepted to indicate the site of synaptic contact in the complex. However a direct synaptic contact between the central element of the synaptic apparatus and the receptor terminal of the sheep could not be excluded since distinct thickenings along the receptor membrane lining the vitread part of the central element were present. In single sections it was not possible to determine the number of processes invaginated in a receptor synaptic body or the origin of the processes. Sjostrand (1958) showed that the central element in a receptor synaptic apparatus of the guinea pig was a bipolar dendrite. Using a combination of Golgi technique and electron microscopy Stell (1965 1967) demonstrated that the lateral elements of goldfish rod and cone synaptic structures were horizontal cell processes and that the central elements (one or more) were bipolar dendrites. Similar findings were reported for the human (Missotten 1965) and the rabbit retina (Sjostrand 1969). It thus appears that the horizontal cell processes are favourably positioned as to a possible influence on the transmission from the receptor to the bipolar cell as also suggested by Stell (1967) by Dowling & Boycott (1967) and by Sjostrand (1969).

So far only one type of horizontal cells were observed in the sheep retina. The primate retina is also considered to have only one type (Polyak 1941 Missotten 1965). Stell (1967) observed two different types of horizontal cells in the goldfish retina however.

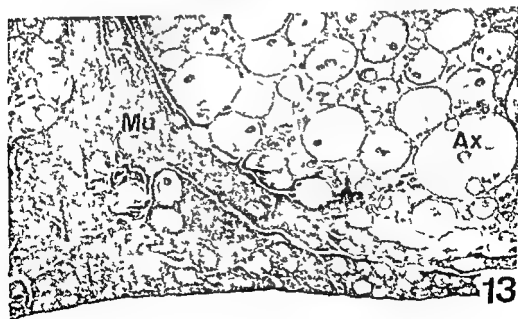
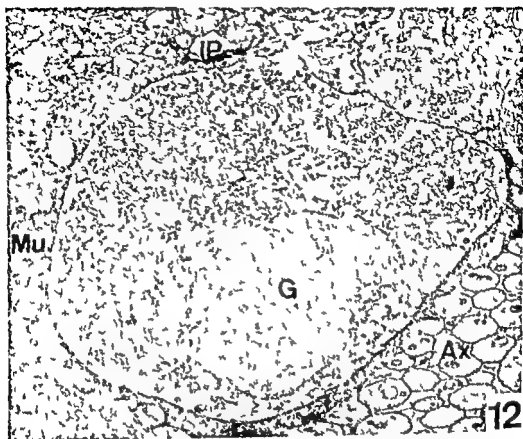
With respect to electron density the bipolar cells of the sheep could be divided into two types dense (dark) ones and less dense (light) ones. Their

Fig 10

A ganglion cell typically containing a large number of ribosomes. IP inner plexiform layer Ax axonal layer Mu Muller cell $\times 7000$

Fig 13

The vitreal surface of the retina where the Muller cell (Mu) foots cover the axons (Ax) $\times 7500$



Figs 12-13

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relation to the receptor cells and the processes of the inner plexiform layer could not be mapped in single sections. Also in the goldfish retina two kinds of bipolar cells were found (Stell 1967). Of the four bipolar types described in light microscopy of the primate retina (Polyak 1941) Missotten (1965) considered it possible to identify three in electron microscopy of the human retina. However the main differences were not found within the inner nuclear layer but in the type of arborization in the plexiform layers. The different bipolar types in the primate retina are considered to be functionally different as to their connections with the other cell layers. Whether this is true for the bipolar cells of the sheep is not known. Some bipolar cells were seen in close relation to horizontal cell bodies or processes (figs 4 and 5). Since tight junctions or specialized regions were not found the significance of this observation is uncertain.

The sheep retina contained a rather large number of amacrine cells. It thus seemed that the lateral connections in the inner plexiform layer were well developed. The indented nucleus observed in the present study is typical for amacrine cells also of the primate retina (Missotten 1965; Dowling & Boycott 1967).

The understanding of the morphology of the inner plexiform layer requires serial sectioning in order to establish the origin of the processes. Using such technique Missotten (1965) and Dowling & Boycott (1967) could identify synaptic ribbon containing processes of the human inner plexiform layer as bipolar terminals. Dowling & Boycott (1967) describe the most typical synapse of the primate inner plexiform layer as a dyad where the bipolar terminal is presynaptic to two processes, one being a ganglion cell dendrite and the other one an amacrine cell process. In Fig. 10 the two processes (opposite the synaptic ribbon) that appear post synaptic to a bipolar terminal in the sheep retina are clearly similar in cytoplasmic content. Thus both processes seem to be of the same type. However in many other cases the two members of a dyad were distinctly different in cytoplasmic content. No definite conclusions can be drawn as long as identification by means of serial sectioning is lacking. In Fig. 11 vesicles are concentrated so as to suggest a synapse back onto a bipolar terminal. The picture resembles the so called reciprocal amacrine bipolar contacts described by Dowling & Boycott (1964) who suggested that such an arrangement could serve as a feedback mechanism responsible for the gain control (adaptation system) which seems necessary in order to allow the eye to discriminate over such a wide range of light intensities.

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VARIA

International Council of Ophthalmology

On occasion of the coming International Congress in Paris May 1974 the Council will issue a new Edition of the *Index Ophthalmologicus* a directory representing a.o. the name and addresses of ophthalmologists in those countries whose national Societies are affiliated in the International Federation of Ophthalmological Societies. These data are collected through the secretaries of the National Societies concerned. Ophthalmologists in smaller locations where no Society exists who are interested to be mentioned in this directory are requested to give their names and addresses directly to the editor Dr C C Copper 42 Coehoornsingel Zutphen Netherlands not later than December 1st 1973

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Preliminary announcement

Conference of Advances in Vitreous Surgery University of California March 19 1974

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PHOTOCOAGULATION TREATMENT OF SOLITARY ANEURYSM NEAR THE MACULA LUTEA

Report of a case

BY

J HUDOMEL and G IMRE

The authors present an indirect photocoagulation method which can terminate arteriolar aneurysm while maintaining the patency of the vessel. This is essential if the aneurysm is located near the macula lutea. Coagulating on the boundary of the lesion, a fibrous scar could generate which by scarring gradually could terminate the aneurysm without obliterating it. In the case reviewed the scarring process lasted about 3 months, the clearing of hard exudates took more than a year, and thereafter visual acuity improved significantly but relative central scotoma remained.

Key words: retina - vascular disorders - photocoagulation - treatment

While microaneurysms or even larger aneurysms are common findings in retinal disorders due to circulatory or metabolic diseases, isolated solitary aneurysms are very rarely seen in the otherwise intact eyeground. According to Duke Elder, these large arteriolar aneurysms are due either to embryological anomalies or to arterial wall disease.

If the aneurysm is peripheral, the visual acuity may remain unaltered for

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Fig 2

The aneurysm immediately after photocoagulation treatment

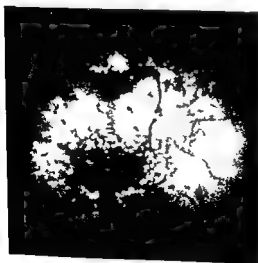


Fig 3

Scar formation 3 months after photocoagulation. Diminishing hard exudates

a long time but in the vicinity of the macula lutea the loss of function due to the exudate and disturbed blood supply would be considerable

If located peripherally treatment could obliterate the aneurysm by direct photocoagulation or diathermy but the same procedure near the macula would result in a gross scotoma furthermore the increased energy needed may cause the vessel to rupture

Therefore in such a situation the direct coagulation of arteriolar aneurysm should be avoided Our goal is to terminate the aneurysm while maintaining the patency of the vessel

This goal would seem attainable if fibrous scar tissue could be generated around the vessel wall thereby encapsulating it the shrinking tissue would then eliminate the dilatation In the following the result of this type of treatment is reviewed

Material and Method

A 56 year old woman complained that the vision in her left eye had been deteriorating steadily for the past 12 months On examination the visual acuity in the left eye was 20/50 Anterior segment lens and vitreous were without pathological finding In the eye-ground (Fig 1) in a temporal and superior position from the macula lutea there

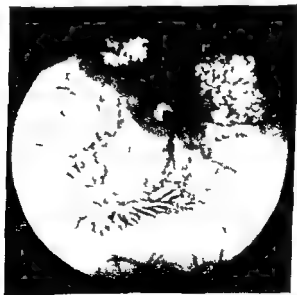


Fig 1

Solitary arteriolar aneurysm about 2 disc diameters above the macula lutea Note hard exudates right in the macula



Fig 5

Fluorescein angiography early venous phase showing patent arteriole within the scar

more than 22 months after photocoagulation Vision in the left eye at that time was 3/15 the hard exudates completely disappeared the visual field examination showed an absolute scotoma in accord with the scar and a relative scotoma which conformed to the area originally bordered by the hard exudates (Fig 6)

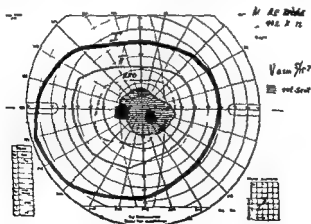


Fig 6

Visual field 2 years after treatment paracentral absolute scotoma indicates the scar and the relative central scotoma conforms to the area of the previous hard exudates



Fig 4

The scar 1 year after photocoagulation. Hard exudates have disappeared

was a large aneurysm on the first branch of the superior arteriole temporalis. In its immediate vicinity there was yellow gray exudate and an irregular ring of hard exudates, the nasal part of which was right in the macula lutea. The signs of moderate arteriosclerosis were also present. Diabetes was excluded and although high blood pressure had been noted previously at that time it was only 140/90 mmHg.

In view of the fact that further deterioration of the functions was to be expected because of the exudates, photocoagulation was decided upon and was performed on November 2, 1970, with a Zeiss Jena 5000 flash photocoagulator. In a 2° field, III grade, with an open aperture, eight coagula were formed and closely bordering the lesion (Fig 2). As usual, retrobulbar anesthesia was not used and this is why one of the coagula somewhat slipped. The aneurysm was not damaged and there was no hemorrhage.

Seven weeks after photocoagulation the aneurysm seemed more dilated than previously and the surrounding area was edematous. After 3 months the upper rim of the aneurysm had shrunk and a whitish scar tissue had formed around it. The number of hard exudates had not diminished and visual acuity was still 5/50 (Fig 3). After 6 months the aneurysm had disappeared. In its place there had developed a scar which was the color of mother of pearl and was slightly pigmented. The number of hard exudates had decreased but vision was still 5/50.

One year after photocoagulation a disc sized, partly pigmented scar was seen in place of the aneurysm. There was slight pigment disturbance in the macula lutea and a few hard exudates were visible (Fig 4). Visual acuity improved to 5/20. Fluorescein angiography also proved that the aneurysm was completely carried (Fig 5) while the arteriole remained patent. The last follow up examination was on October 15, 1971.

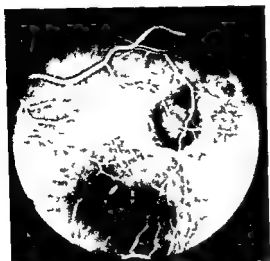


Fig 5

Fluorescein angiography early venous phase showing patent arteriole within the scar

more than 97 months after photocoagulation Vision in the left eye at that time was 5/157 the hard exudates completely disappeared the visual field examination showed an absolute scotoma in accord with the scar and a relative scotoma which conformed to the area originally bordered by the hard exudates (Fig 6)

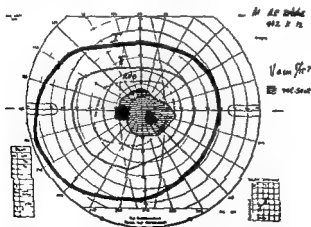


Fig 6

Visual field years after treatment paracentral absolute scotoma indicates the scar and the relative central scotoma conforms to the area of the previous hard exudates

Conclusion

In this case therefore by photocoagulating the immediate area the aneurysm was gradually scarred while the arteriole remained patent. The scarring was completed within six months which coincides with our experience with Coats disease after diathermy or photocoagulation therapy. After the absorption of the exudates visual acuity improved significantly however the retina damaging effect of the exudates is attested to by the remaining relative scotoma.

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CLINICAL EXPERIENCE WITH PROPRANOLOL IN THE TREATMENT OF GLAUCOMA

BY

ARNE ÖHRSTRÖM

The literature on the use of propranolol (Inderal® ICI) in ophthalmology is surveyed and the successful use of the drug in the treatment of increased intraocular pressure is documented by four illustrative case reports

Key words: propranolol - Inderal® - glaucoma - adrenergic β blocker

Propranolol (Inderal® ICI) has been available since the middle of the 1960's and more than 2000 reports have been published on its effect in cardiac arrhythmia, angina pectoris, thyreotoxicosis, hypertension and nervous tension. Propranolol blocks the β adrenergic receptors and its effect in the above diseases is well documented.

Propranolol also decreases the intraocular pressure (IOP). Philips et al (1966) were the first to describe this effect. They found that 10 mg i.v. or 3-40 mg a day by mouth reduced the IOP in seven patients with glaucoma. Cote & Drance (1968) reported a similar effect of 20-50 mg a day by mouth on open angle glaucoma in 26 patients though the response tended to decrease with time. Buccis et al (1968) found that topical application of 1% solution of propranolol markedly lowered the IOP in 10 normotensive eyes and in 31 eyes with simple chronic glaucoma. El Shewy & Amin (1969) reported a similar effect on normal and glaucomatous eyes in 26 patients; the drug

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having been given systemically and retrobulbarly. Valz & Phillips (1970) treated rabbits and seven patients with glaucoma with propranolol and found that it not only reduced the IOP in both. Musari et al (1971) found that topical administration of 2% solution of propranolol depressed the IOP. They thought that the reduction was due to an anaesthetic effect of the drug. According to Bietti (1972) a 2% solution given topically in patients with glaucoma decreases the IOP especially when given over a long period of time or when combined with pilocarpine. This treatment has no undesirable effect on the size of the pupils or vision or on corneal sensitivity. The present paper concerns some of the indications for propranolol and its therapeutic effect as illustrated in four clinical cases.

Selection of the Patients and Dosage

At the Department of Ophthalmology, Malmö General Hospital, propranolol has been tried for 12 years as a supplementary drug in the treatment of glaucoma as a last resource to avoid operation or when operation has failed to reduce the IOP satisfactorily.

Propranolol was given by mouth in tablets in doses of 20-40 mg 4 times daily. Since obstructive pulmonary disease and uncompensated heart disease as well as AV block II-III contraindicate treatment with propranolol the patient's history was carefully studied for cardiac and pulmonary diseases, and if necessary physical examination was supplemented by ECG and chest X-ray.

Case Report

Case 1 The patient was a 58-year-old woman. In 1970 she developed a bilateral senile cataract which was extracted in the left eye. In 1971 she had iridocyclitis in the right eye for a month. Annual follow-up afterwards showed nothing remarkable. In 1972 the iridocyclitis recurred on the right eye and the IOP was then 80-90 mmHg. The inflammation responded to steroid therapy but the pressure remained around 35 mmHg. Cycloidalysis was successful. Two months later the cataract was extracted intracapsularly. The operation was complicated by vitreous loss. The post-operative course was uneventful until the 18th day when the patient began to complain of pain, and the tension was then found to be 40 mmHg (Fig. 1). The anterior chamber had disappeared and the vitreous was lying against the cornea. Treatment with acetazolamide and glycerol had a moderate effect. Two days later pilocarpine

Propranolol in Treatment of Glaucoma

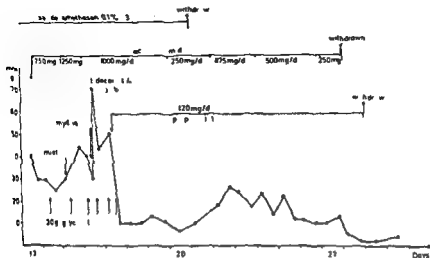


Fig 1

Case 1 Course of treatment and its effect on intraocular pressure (IOP) from the 13th day postoperatively until the patient was discharged with full vision and normal IOP

was tried but it only increased the tension. The following day dilatation of the pupil to interrupt the vitreous block was followed by an immediate further increase in the IOP to 60 mmHg. The pressure peak was however reduced by 1.5 ml lidocaine retrobulbally combined with a dose of glycerol *per os*. The next day treatment was supplemented by propranolol in a dose of 40 mg 4 times daily and within 4 hours the tension fell to 10 mmHg. The anterior chamber and the vitreous block appeared unchanged. Acetazolamide could be reduced and on the 27th day the anterior chamber was of normal depth. All the drugs were withdrawn and the patient left hospital with full vision and normal IOP.

Case 2 The patient was an 80 year old man. For the past 25 years he had had left sided post-traumatic amaurosis. In 1969 open angle glaucoma of the right eye was diagnosed. The pressure responded favourably to carbacholine in a dose of 3% 3 times daily (Fig 2). Later this treatment had to be supplemented with acetazolamide in a dose of 100 mg twice daily. The IOP remained satisfactory for 1 year after which it again rose. Acetazolamide was increased to 150 mg 3 times daily without effect. Propranolol was then given 20 mg 4 times daily. The tension returned to a satisfactory level and it remained so. For some unknown reason the dose was reduced by a general practitioner to 10 mg twice daily but the IOP continued to remain satisfactory.

Case 3 The patient a 70 year old man had had absolute glaucoma of the right eye since 1940. The left eye had been normal up to 1968 when the tension was found to be elevated. It responded favourably to pilocarpine 3 times daily and remained

having been given systemically and retrobulbarly. Vale¹ treated rabbits and seven patients with glaucoma with propranolol and found that it notably reduced the IOP in both. Musini et al.² found that topical administration of 2% solution of propranolol depressed the IOP. They thought that the reduction was due to an anesthetic effect. According to Bieth³ (1972) a 2% solution given topically in glaucoma decreases the IOP especially when given over a long time or when combined with pilocarpine. This treatment has no effect on the size of the pupils or vision or on corneal sensitivity. Proper concerns some of the indications for propranolol and its effect as illustrated in four clinical cases.

Selection of the Patients and Dosage

At the Department of Ophthalmology, Malmö General Hospital, propranolol has been tried for 1½ years as a supplementary drug in the treatment of glaucoma as a last resource to avoid operation or when operation has failed to reduce the IOP satisfactorily.

Propranolol was given by mouth in tablets in doses of 20–40 mg daily. Since obstructive pulmonary disease and uncompensated heart failure as well as AV block II–III contraindicate treatment with propranolol, the patient's history was carefully studied for cardiac and pulmonary disease and if necessary physical examination was supplemented by ECG and X-ray.

Case Report

Case 1 The patient was a 63 year old woman. In 1960 she developed a bilateral senile cataract which was extracted in the left eye. In 1962 she had iridocyclitis in the right eye for a month. Annual follow up afterwards showed nothing remarkable. In 1972 the iridocyclitis recurred on the right eye and the IOP was then 35 mmHg. The inflammation responded to steroid therapy but the pressure remained around 35 mmHg. Cyclodialysis was successful. Two months later the cataract was extracted intracapsularly. The operation was complicated by vitreous loss. The postoperative course was uneventful until the 10th day when the patient began to complain of pain and the tension was then found to be 40 mmHg (Fig. 1). The anterior chamber had disappeared and the vitreous was lying against the cornea. Treatment with acetazolamide and glycerol had a moderate effect. Two days later pilocarpine

Propranolol in Treatment of Glaucoma

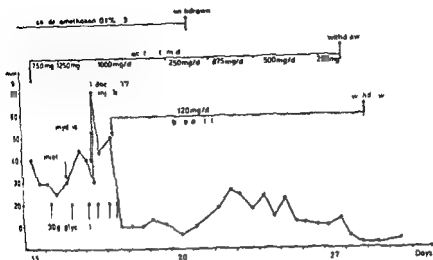


Fig 1

Case 1 Course of treatment and its effect on intraocular pressure (IOP) from the 18th day postoperatively until the patient was discharged with full vision and normal IOP

was tried but it only increased the tension. The following day dilatation of the pupil to interrupt the vitreous block was followed by an immediate increase in the IOP to 30 mmHg. The pressure peak was however reduced by 15 ml lidocaine retrobulbarly combined with a dose of glycerol per os. The next day treatment was supplemented by propranolol in a dose of 40 mg 4 times daily and within 4 hours the tension fell to 10 mmHg. The anterior chamber and the vitreous block appeared unchanged. Acetazolamide could be reduced and on the 27th day the anterior chamber was of normal depth. All the drugs were withdrawn and the patient left hospital with full vision and normal IOP.

Case 1 The patient was an 80 year old man. For the past 9 years he had had left sided post traumatic amaurosis. In 1969 open angle glaucoma of the right eye was diagnosed. The pressure responded favourably to carbacholine in a dose of 3% 3 times daily (Fig. 1). Later this treatment had to be supplemented with acetazolamide in a dose of 1 mg twice daily. The IOP remained satisfactory for 1 year after which it again rose. Acetazolamide was increased to 195 mg 3 times daily without effect. Propranolol was then given 40 mg 4 times daily. The tension returned to a satisfactory level and it remained so. For some unknown reason the dose was reduced by a general practitioner to 10 mg twice daily but the IOP continued to remain satisfactory.

Case 3 The patient a 7 year-old man had had absolute glaucoma of the right eye since 1963. The left eye had been normal up to 1968 when the tension was found to be elevated. It responded favourably to 1% pilocarpine 3 times daily and remained

having been given systemically and retrobulbally. Vale & Phillips (1960) treated rabbits and seven patients with glaucoma with propranolol and found that it notably reduced the IOP. In both Musini et al (1961) found that topical administration of 2% solution of propranolol depressed the IOP. They thought that the reduction was due to an anesthetic effect of the drug. According to Bieth (1972) a 2% solution given topically in patients with glaucoma decreases the IOP especially when given over a long period of time or when combined with pilocarpine. This treatment has no undesirable effect on the size of the pupils or vision or on corneal sensitivity. The present paper concerns some of the indications for propranolol and its therapeutic effect as illustrated in four clinical cases.

Selection of the Patients and Dosage

At the Department of Ophthalmology, Malmö General Hospital, propranolol has been tried for 1½ years as a supplementary drug in the treatment of glaucoma as a last resource to avoid operation or when operation has failed to reduce the IOP satisfactorily.

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Case Report

Case 1. The patient was a 3-year-old woman. In 1960 she developed a bilateral senile cataract which was extracted in the left eye. In 1965 she had iridocyclitis in the right eye for a month. Annual follow-up afterwards showed nothing remarkable. In 1962 the iridocyclitis recurred on the right eye and the IOP was then 40–50 mmHg. The inflammation responded to steroid therapy but the pressure remained around 35 mmHg. Cyclodialysis was successful. Two months later the cataract was extracted intracapsularly. The operation was complicated by vitreous loss. The post-operative course was uneventful until the 13th day when the patient began to complain of pain and the tension was then found to be 40 mmHg (Fig 1). The anterior chamber had disappeared and the vitreous was lying against the cornea. Treatment with acetazolamide and glycerol had a moderate effect. Two days later pilocarpine

Propranolol in Treatment of Glaucoma

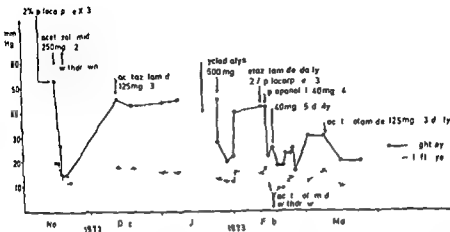


Fig 4

Case 4 Course of treatment and its effect on IOP during a period of 5 months

He was first seen at our department in November 1972 (Fig 4) with mild inflammation of the right eye and an IOP of 55 mmHg. The iris was pale and slightly atrophic. Posterior cortical cataract was present. The left eye appeared normal. He was first treated with acetazolamide until the pressure became normal. He was then sent home with only 2% pilocarpine 3 times daily. At the next follow up examination the tension was again high and he was again given acetazolamide but now with only little effect. All drugs were then withdrawn and a cyclodialysis was performed. Six days after the operation the eye was painful and the tension was 45 mmHg. Acetazolamide in a dose of 500 mg a day had some effect but the IOP persisted at about 40 mmHg. Addition of pilocarpine 2% 3 times daily had no demonstrable effect. Propranolol in a dose of 40 mg 4 times daily was tried and the tension promptly fell to 10 mmHg. Since the IOP in the mornings was still somewhat high the dose was increased to 40 mg 5 times daily. But the acetazolamide was not tolerated and was therefore withdrawn. The pressure again rose to 30 mmHg. Treatment with acetazolamide was thus resumed in a dose of 125 mg 3 times daily after which the pressure remained at about 10 mmHg during treatment with 2% pilocarpine 3 times, acetazolamide 125 mg 3 times and propranolol 40 mg 5 times daily.

Discussion

The cases reported above illustrate the depressive effect of propranolol on the IOP. We used propranolol in a further 20 cases of glaucoma and found it to have a beneficial effect. Since many of the patients were treated with a combination of miotics, acetazolamide and propranolol it was not possible to assess the effect of propranolol alone.

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CLINICAL AND FLUORESCEIN ANGIOGRAPHIC FINDINGS OF ACUTE MULTIFOCAL CENTRAL SUBRETINAL INFLAMMATION

BY

LEILA LAATIKAINEN and HEIKKI ERKKILÄ

Three female patients with acute multifocal subretinal central lesions and with almost complete recovery of macular function are presented. The findings and the course of the disease are very similar to acute posterior multifocal placoid pigment epitheliopathy described initially by Gass in 1968. Etiology of the disease could not be determined but the history of solar exposition in two patients suggests the possibility of an exogenous factor.

In the presented cases fluorescein angiographic findings suggest primary alterations in the choriocapillaris rather than in the pigment epithelial cells.

Key words: retina - acute posterior multifocal placoid pigment epitheliopathy - fluorescein angiography

Acute posterior multifocal placoid pigment epitheliopathy was initially described by Gass (1969a) in three healthy young female patients. The etiology of the disease could not be determined but the clinical and angiographic findings and the course of the lesions suggested that they represent an acute pigment epithelial cellular response to some local injurious agent rather than a choroidal infiltration (Gass 1969a,b).

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The reason why the patients were treated with more than one drug was that propranolol was resorted to in those cases where the other drugs had failed to produce the desired effect. As a rule the dose used was kept moderate i.e. about 160 mg a day in order to avoid the occurrence of bradycardia. Another reason for keeping the dosage of propranolol low was to prevent a pronounced change in the blood pressure affecting the ocular circulation and impairing the blood supply to the optic nerve. Therefore the dose never exceeded 300 mg a day. In contrast to acetazolamide with its well known common side effects propranolol produced no undesired reactions except mild diarrhoea in one case.

The mechanism by which propranolol lowers the IOP is not known. Vale & Phillips (1970) assumed that a blockade of the β adrenergic receptors increases the outflow of aqueous humour and that the anti arrhythmic properties of propranolol cause a reduction in the production of this fluid. The findings in our first case (Fig. 1) in which propranolol decreased the IOP in an eye with flat anterior chamber suggest mainly a decrease in the production of the aqueous humour. In our opinion propranolol may be regarded as a valuable addition to depressants of IOP and may prove useful in longterm treatment of glaucoma.

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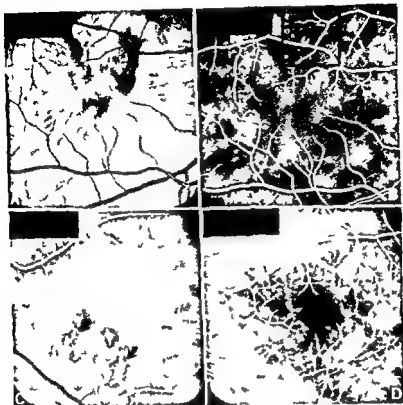


Fig 1

Case No 1 in the acute stage. Right eye. Numerous small confluent grayish lesions are seen in the macular area (A). Angiogram shows hypofluorescence of the lesions in the early venous phase (B). Left eye. Filling of some large choroidal vessels is seen in the retinal arterial phase (C arrow). In the venous phase late but deficient filling of the choriocapillaris is seen (D). Retinal capillaries are not affected. The square in Figs 1-4 indicates an area to be compared in the various stages of the disease.

By the diffuse fluorescence of the choriocapillaris. In the retinal venous phase there was gradual staining of the lesions. Hyperfluorescent areas were not seen in the acute stage. Larger retinal vessels or capillaries were not affected and there was no fluorescein leakage into the retina.

Resolution of the lesions was rapid and no new lesions could be seen. After 100 days nonfluorescent areas in the angiogram were smaller and some of them had totally disappeared (Fig 7).

There were hyperfluorescent areas at the borders of the lesions in the retinal venous phase and marked staining of the damaged tissues in the late angiogram due to alterations of the choriocapillaris and beginning depigmentation of pigment epithelial cells.

Van Buskirk et al (1971) reported a young female patient with erythema nodosum and the same eye features as those of Gass (1968). These authors interpreted the lesions to be more suggestive of a focal choroidal vasculopathy than a primary pigment epitheliopathy. Schlaegel (1969, 1972) described placoid pigment epitheliopathy together with serpiginous choroiditis because of many similarities between these diseases.

The case reports of the patients with acute multifocal central subretinal lesions are now presented with special attention to the fluorescein angiographic findings in the various stages of the disease.

Case No. 1

It is a 24 year old woman was initially examined on June 16, 1970 with a 1 day history of small paracentral scotomas first in the right eye and then 2 days later in the left eye as well. On the day before the onset of the symptoms she had been exposed to extremely bright sunshine for many hours. The patient was subject to episodes of allergic rhinitis and erythema nodosum with unknown etiology had been diagnosed 17 years earlier.

On examination visual acuity in the right eye was 0.4 and in the left eye 0.5. Ophthalmoscopic examination revealed multiple confluent grayish subretinal lesions in the posterior pole of both eyes especially in the macular areas. A few cells were found in the vitreous.

General physical examination, chest and paranasal sinus X-ray films as well as orthopantomographs were normal. Sedimentation rate was 20, blood cell count, electrophoresis, immunoelectrophoresis, antistreptolysin and antistaphylococcal titers were normal. Latex fixation, Waaler-Rose and cardiolipin were negative, no diagnostic changes were found in virus antibody titers. A tuberculin skin test was positive.

The patient was treated with antibiotics and with systemic prednisone initially a dose of 60 mg daily for about two months. Remarkable resolution of the lesions with fine pigment mottling was seen within 2 weeks. Visual acuity of 1.0 was recovered in the right eye after 4 weeks and 1.3 in the left eye after 6 weeks. Some metamorphopsia was however present.

Follow up of 2.5 years has revealed no additional visual complaints. Visual acuity is 1.6 in both eyes, color vision with Panel D 15 test is normal, no visual field defects can be found with the Friedmann central field analyzer. A slight distortion of some vertical and horizontal lines is however noted on the Amsler grid test in both eyes. An electrooculogram shows low but not clearly pathological values (1.0° in the right, 1.50° in the left eye). EKG is normal in both eyes.

Fluorescein angiographic findings: In the acute stage (2 weeks after the onset of the symptoms) there were numerous small partly confluent nonfluorescent areas in the posterior pole (Fig. 1). Hypofluorescence of the lesions might be caused by swelling of the pigment epithelial cells. Fig. 1 shows however delayed and deficient filling of the choriocapillaris because some major choroidal vessels were seen at the site of the lesion in the retinal arterial phase (Fig. 1C). Otherwise choroidal vessels were obscured

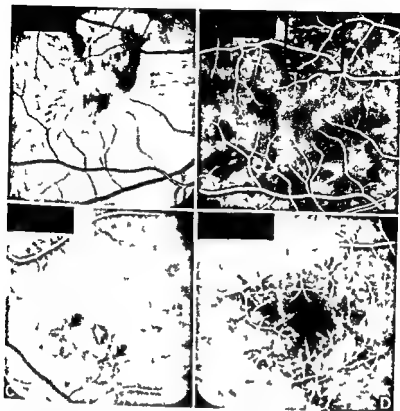


Fig 1

Case No 1 in the acute stage Right eye Numerous small confluent grayish lesions are seen in the macular area (A) Angiogram shows hypofluorescence of the lesions in the early venous phase (B) Left eye Filling of some large choroidal vessels is seen in the retinal arterial phase (C arrow) In the venous phase late but deficient filling of the choriocapillaris is seen (D) Retinal capillaries are not affected The square in Figs 1-4 indicates an area to be compared in the various stages of the disease

by the diffuse fluorescence of the choriocapillaris In the retinal venous phase there was gradual staining of the lesions Hyperfluorescent areas were not seen in the acute stage Larger retinal vessels or capillaries were not affected and there was no fluorescence leakage into the retina

Resolution of the lesions was rapid and no new lesions could be seen After 10 days nonfluorescent areas in the angiogram were smaller and some of them had totally disappeared (Fig 2)

There were hyperfluorescent areas at the borders of the lesions in the retinal venous phase and marked staining of the damaged tissues in the late angiogram due to alteration of the choriocapillaris and beginning depigmentation of pigment epithelial cells

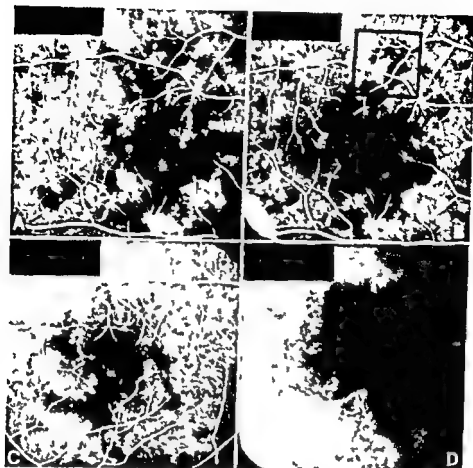


Fig. 2

Case No. 1 in the subacute stage: right eye (A-B) and left eye (C-D). Hypofluorescent areas are fewer in number and smaller in diameter than in the acute stage. Slight hyperfluorescence is seen in the recovering (peripheral) parts of the lesions (A-C). In 15 minutes (D) marked staining of the lesions is seen.

Three to four months after the onset of the symptoms most of the lesions were inactive showing fine pigment clumping in the middle of the lesions surrounded by hyperfluorescent zone due to depigmentation of the pigment epithelial cells (Fig. 3). Marked staining of a few lesions however was still seen in the retinal venous phase.

Two and a half years after the acute stage fluorescein angiography showed several small hyperfluorescent areas of depigmentation with fine pigment clumping. There were no signs of activity and no alterations could be seen in the retinal capillaries around the scars (Fig. 4).

Case No. 2

UN: a 25 year old woman was first seen on August 1, 1960 with a 7 day history of blurred vision in both eyes. For 2 weeks the patient had taken both usual sunlight

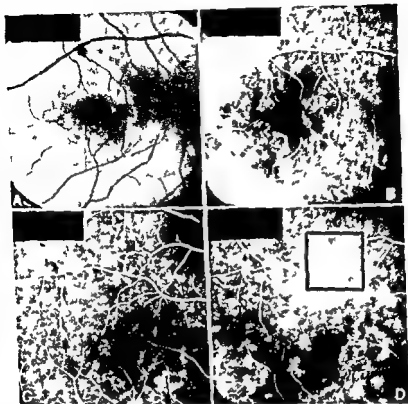


Fig 3

Case No 1 Left eye (A-B) three months and right eye (C-D) four months after the onset of the symptoms Fig A and B show the remarkable discrepancy in the ophthalmoscopic and angiographic findings at the stage of recovery Intense hyperfluorescence in the venous phase indicates activity in some of the lesions (B D square)

and artificial sun every day without protecting her eyes carefully Her general health was good and there was nothing remarkable in her previous history

On examination visual acuity in the right eye was finger counting 5 meters and in the left eye finger counting 25 meters There were no signs of inflammation except for gray white subretinal slightly elevated confluent lesions in the posterior pole of both eyes There was however no serous detachment of the retina

Sedimentation rate was 40 and there was mild leukocytosis (8400) the other etiological examinations mentioned in the first case report showed normal results

This patient was also treated with systemic prednisone for 5 weeks with an initial dose of 60 mg every day combined with antibiotics The lesions showed rapid resolution and no new active lesions could be noted during the treatment Visual acuity of 10 was recovered in the right eye in 7 weeks and in the left eye in 15 weeks



Fig 4

Case No 1 after 25 years follow up time. Numerous hyperfluorescent spots due to depigmentation of the pigment epithelial cells and pigment clumping are seen in both eyes (A, B). The areas of depigmentation are smaller than the hyperfluorescent lesions in the recovering stage (square).

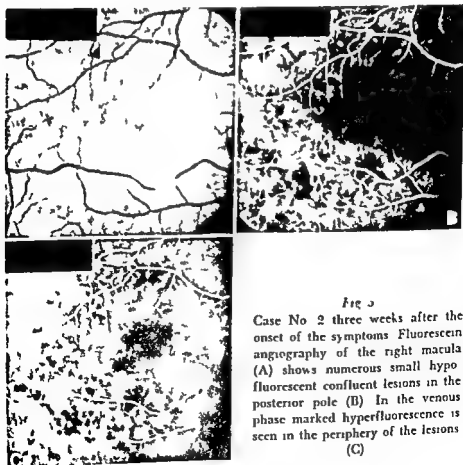


Fig 5

Case No 2 three weeks after the onset of the symptoms. Fluorescein angiography of the right macula (A) shows numerous small hypo-fluorescent confluent lesions in the posterior pole (B). In the venous phase marked hyperfluorescence is seen in the periphery of the lesions (C).



Fig 6

Case No 2 after 25 years follow up time. Before fluorescein injection slight pigment dispersion is seen in the macular area (A). Angiogram shows small hyperfluorescent scars suggesting pigment clumping and depigmentation of the pigment epithelial cells (B, C).

On control examination 25 years after the onset of the symptoms visual acuity was 13 in the right eye and 10 in the left eye. Ophthalmoscopy revealed slight pigment dispersion in both macular areas, one small relative paracentral scotoma in the left eye, and color vision and EOG were normal in both eyes.

Fluorescein angiographic findings. The first fluorescein angiography was performed 5 weeks after the onset of the symptoms. There were several small nonfluorescent lesions surrounded by hyperfluorescent areas in the later phases of angiogram (Fig 5). The findings were very similar to those seen in the subacute stage in Case 1. Clearing of the lesions caused some pigment clumping surrounded by depigmentation (Fig 6). In Case 2 the final scars are less confluent and slightly more heavily pigmented than those in Case 1.

Case No 3

Black 5-year-old woman was initially examined on July 19, 1961, because of an acute paracentral scotoma in the left eye. On examination visual acuity in the right eye was 11 and in the left eye 10. On ophthalmoscopy multiple small grayish subretinal

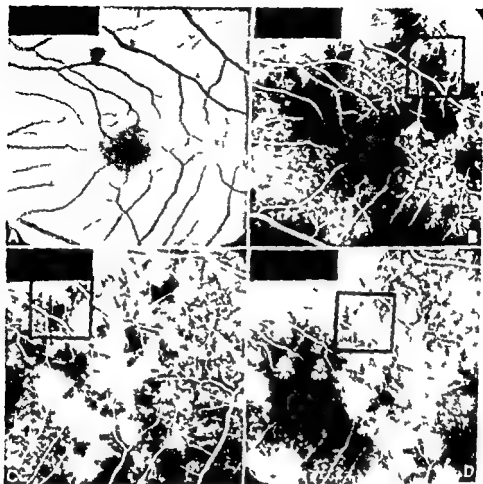


Fig 7

Case No 3 in the acute stage of the disease. Angiogram of the grayish lesions of the posterior pole (A) shows late filling of the choriocapillaris (B-D squares). Marked hyperfluorescence in the venous phase (C) indicates more diffuse affection of the choriocapillaris than of the pigment epithelium.

lesions were seen in the left posterior pole otherwise the examination revealed nothing remarkable.

The general health was good. Sedimentation rate was 5 and white blood cell count totalled 8600. The chest and paranasal sinus X rays were normal. A tuberculin skin test was positive. More complete etiologic evaluations were not performed in this case.

Visual acuity returned to 1/6 and subjective symptoms disappeared within 4 weeks without any treatment. One year later visual acuity in both eyes was 1/6, faint pigment dispersion was seen in the left macular area, color vision, visual fields, ERG and EOG were normal in both eyes.

Fluorescein angiographic findings. In the acute stage there were numerous occasionally confluent nonfluorescent lesions in the posterior pole in the retinal arterial

phase (Fig 4) In the retinal venous phase these lesions began to stain from the periphery and numerous hyperfluorescent areas were seen around them as well In late angiogram both the initially nonfluorescent lesions and the surrounding hyperfluorescent areas showed marked staining These findings suggest that there was delayed filling of the choriocapillaris at the site of the lesions but alterations of the choriocapillaris were also present in the surrounding areas leading to abnormal staining of the tissues After recovery there were only a few small hyperfluorescent spots due to depigmentation of the pigment epithelial cells

DISCUSSION

There are many similarities between these patients and those reported by Gass in 1968 as acute posterior multifocal placoid pigment epitheliopathy young female patients with acute loss of central vision secondary to subretinal macular lesions The lesions cleared rapidly with minimal scar formation accompanied by nearly complete recovery of the macular function

Gass (1969a b) suggested that in his cases primary alterations took place in the pigment epithelium rather than in the choroid Fluorescein angiographic findings of our patients however suggest primary involvement of the choriocapillaris In one case filling of the large choroidal vessels - normally obscured by the choriocapillaris - could be seen in the retinal arterial phase (Fig 1) Filling of the large choroidal vessels has not been visible in cases reported earlier (Gass 1968 a b Hyvarinen et al 1969 Van Buskirk et al 1971) It is possible that in most cases secondary swelling of the pigment epithelial cells is intense enough to obscure all choroidal fluorescence In another case the area of damaged choriocapillaris seems to be remarkably larger than the area of pigment epithelium that was affected (Fig 7) Staining of the lesions in the retinal venous phase began from the periphery and might be due to slow filling of the damaged choriocapillaris although diffusion of the dye from the surrounding areas may occur as well

At the stage of resolution all three cases showed normal filling of the choriocapillaris in the retinal arterial phase In the venous phase marked hyperfluorescence of the lesions was seen however suggesting abnormal leakage of the recovering choriocapillaris After resolution of the lesions hyperfluorescent areas were still seen but these were smaller than in the subacute stage and were due to depigmentation of the pigment epithelium

Etiology of the placoid pigment epitheliopathy is not known (Schlaegel 1969) Maumenee (1970) Gass (1968) suggested some infectious or toxic agent Two patients now reported had slightly elevated sedimentation rates but no other signs of infection could be found Furthermore both the clinical and

angiographic findings and the benign course of the disease differed from those in the progressive macular disease of possible viral etiology reported by Vinnars et al (1971). One of our patients had suffered from erythema nodosum 12 years previously. Van Buskirk et al (1971) reported one case of simultaneous occurrence of placoid pigment epitheliopathy and erythema nodosum. The significance of the very similar history of sunlight or strong UV light exposure in two of our patients is not known. Some accidental exogenous etiological factor may, however, be present because both eyes were simultaneously and symmetrically involved and no new lesions could be found after the first examination. In the latter respect the course of the disease may be affected by the prednisone treatment employed.

The course of the multifocal placoid pigment epitheliopathy seems to be unrelated to therapy (Cass 1969). The effectiveness of the prednisone therapy in the resolution process of our cases cannot be certain either because in one of these patients (Case 3) rapid recovery took place without any treatment having been given.

Acknowledgment

This investigation was supported by a grant from the Silmäsäätiö Foundation.

Addendum

Since the submission of this paper for publication three reports concerning placoid pigment epitheliopathy were published in the *British Journal of Ophthalmology* (Vol 56 No 12 Deutman et al pp 863-874; Kirkham et al pp 875-880 and Bird & Hamilton pp 881-886). In all of them a primary affection of the choroidal vasculature was also suggested in spite of a slightly different interpretation of the fluorescein angiograms.

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THE DISTRIBUTION OF LIGHT SCATTERED FROM THE RABBIT'S CORNEA

BY

J I LINDSTRÖM T FEUK and B TENGROTH

Under normal conditions the mammalian cornea is highly transparent over a broad wavelength range. In the wavelength range of the highest receptor sensibility, i.e. 5000-6000 Å, the cornea transmits more than 90% of the incident radiation intensity. Recent measurements on the rabbit's cornea show that the transmission at 6000 Å is about 94%, the residual 6% being scattered or absorbed. Under pathological conditions the scatter from different parts of the cornea may change drastically. The purpose of this work was to measure the intensity of back scattered light as a function of depth in the rabbit's cornea during changes in the intraocular pressure. It was found that the anterior half of the stroma always gives rise to stronger scatter than the posterior half. Increasing intraocular pressure usually increases the scatter from the anterior side of the stroma while scatter from the posterior side is essentially unaffected. The behaviour is in accordance with theoretical expectations.

Key words: cornea - light scatter - corneal edema - laser - transparency - rabbit

The anatomical properties of the mammalian cornea are well known; see for example Maurice (1957). In brief the cornea is composed of five layers schematically shown in Fig. 1. The major part of the corneal section is made up by

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stroma. The stroma is composed of lamellae 1.5–2.5 μm thick and 2–3 mm broad running over the whole diameter of the cornea. The lamellae are made up of collagen fibrils surrounded by an amorphous ground substance. The fibrils run parallel to each other in the lamellae. In an electron microscope the fibrils seem to be approximately circular in section with a diameter of 200–300 Å and with a mean center to center distance of ≈ 600 Å probably arranged in a hexagonal lattice like structure. The exact origin of the forces separating the fibrils from each other is unknown but it is supposed that mucopolysaccharides in the ground substance are involved in the process (Maurice 1960).

Normally the intracorneal pressure is about –50 mmHg and the intraocular pressure about +20 mmHg that is the normal fluid pressure difference over the endothelial barrier is around 70 mmHg.

Under these conditions the cornea is highly transparent. The transparency is explained by Maurice (1957) in terms of a lattice like geometrical regularity of the fibrils within each lamella. This proposal has been further developed and analysed in quantitative detail by Feuk (1970) and others (Benedek 1971) (Hart & Farrell 1969). Feuk has shown theoretically that the degree of fibril regularity required for normal transparency is consistent with actual micrographic pictures (Goldman 1970) of the lamellae cross sections. He has also shown that the light intensity scattered from the cornea should increase rapidly when the fibril regularity becomes distorted.

Berkley (1967) has shown theoretically that the stroma tissue is more compressed on the posterior side than on the anterior side. This leaves more room for geometrical fibril irregularities on the anterior side and it is therefore reasonable to expect stronger scatter from the anterior side than from the posterior side even under normal conditions. The present experimental results

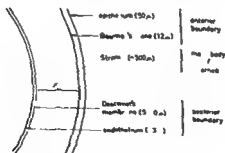


Fig. 1
Schematic drawing of the mammalian cornea

are consistent with this expectation. Increased intraocular pressure would further decompress the stromal tissue on the anterior side according to Berkley which should give increased scatter from this side. The posterior side becomes more compressed when the intraocular pressure increases which should not affect the scatter very much. The present measurements are in agreement also with these predictions.

Apparatus

The experimental apparatus used to measure the light scattering versus corneal depth is rather complex. The complexity is mainly due to the fact that the scattered light intensity from the cornea is very small and that the corneas must be kept in a proper biological environment during the measurements. It is not the aim of this paper to describe the equipment in great detail but rather to give enough information to the reader that he may easily interpret our results. For further information about the detailed construction of the apparatus the reader is referred to Lindström (1968) and Lindström (1973). The goal was to make an instrument allowing many different parameters to be varied in a controlled way.

As illumination source we chose a low powered He Ne laser. In addition to the high intensity of the laser light theoretical calculations are much easier to perform if the illumination source is monochromatic as is the laser. Spatial coherence however caused some problems which had to be solved (see below). Although we have a larger amount of light focused onto the cornea we must have a very sophisticated detection system since the detected signal is only about 10^{-15} W.

An optical bench serves as the base for most of the optical equipment. The

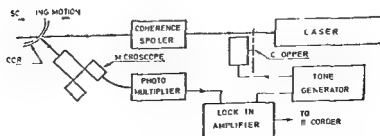


Fig 2

Block diagram showing the illumination and detection system

corneas are mounted in such a way that they can be moved with a geared motor about 0.1 mm along the bench. The light beam from the laser is focused at the same spot all the time relative to the optical bench and the microscope used to detect the scattered light. Thus when the cornea is moved along the bench recordings of the scattered light intensity versus corneal depth can be obtained.

A block diagram of the illumination and detection system is shown in Fig. 2. A 6 mW laser at 633 nm illuminates the cornea. The laser beam is focused into a narrow slit in the cornea using a cylindrical lens. The light beam has a minimum cross section of 0.035×2 mm and contains essentially the whole laser output power. The cornea is mounted in a movable container in order to position the cornea or to make a scanning motion.

The illumination section of the cornea is viewed along the optical axis of the eye at 45° from the illuminating beam and is magnified $10\times$ by a microscope system forming a real image. In the image plane is placed an optical light guide with its end formed as a slit with dimensions 0.035×2 mm (see Fig. 3). The real image may also be observed using a second eyepiece on the microscope. Thus it is possible to make continuous observation of the sampled corneal region. At the same time photographs may also be taken with a camera connected to the microscope.

The scattered light collected by the light guide is detected by a high sensitivity photomultiplier (Philips XP 1002) followed by a phase sensitive detector whose output is presented on a recorder. The resolution obtained is about $50\text{ }\mu\text{m}$ and is limited only by the width of the laser slit lamp beam.

Without special precautions the high degree of spatial coherence of the laser light and the slow drifting of large scattering centers in the corneas would make our signal to noise ratio very low and thus make the registrations unusable. The scattering centers (probably cells) would give rise to a speckle pattern due to interference producing strong maxima and minima. In the microscope this shows up as dark spots slowly wandering across the observed area. This dif-

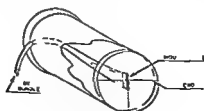


Fig. 3

The picture shows the modified eyepiece with a flattened fiber optic guide in the image plane.

are consistent with this expectation. Increased intraocular pressure would further decompress the stromal tissue on the anterior side according to Berkley, which should give increased scatter from this side. The posterior side becomes more compressed when the intraocular pressure increases which should not affect the scatter very much. The present measurements are in agreement also with these predictions.

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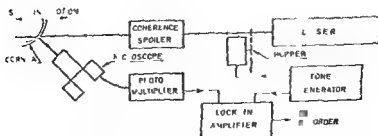


Fig 2

Block diagram showing the illumination and detection system

The rotating glass plate will produce a 9% intensity modulation of the laser beam when it is linearly polarized. In applications where these periodic losses are disturbing one can either use circular polarization antireflection coatings or a thicker plate at smaller angle to the beam. In Fig 5 is shown a recording from a circular opalescent glass plate with and without coherence spoiler. An improvement in signal to noise ratio of more than 10 is observed. With the rotating beam technique the signal to noise ratio in the signal recorded from the scattered light from the cornea is about 50.

The phase sensitive detector used for measuring the current from the photomultiplier requires a chopped light beam and a reference signal with a frequency identical to or at a harmonic of the chopper frequency. The light beam from the laser was chopped using an ordinary chopper wheel driven by a small synchronous motor. The generator driving the motor also supplies the reference signal to the phase sensitive detector. The chopper frequency was chosen to be 13 Hz.

The laser output power was monitored on an oscilloscope using a second photomultiplier as a detector. An uncoated optical flat deflects part of the laser beam onto the cathode of this photomultiplier. The laser was always allowed to stabilize its output power for at least one hour after it had been switched on before any measurements started.

The excised corneas were mounted in a special holder see Fig 6. The holder allows the intraocular pressure to be varied while at the same time a nutrition solution (TC 193) could slowly pass by the endothelial part of the cornea. The holder with the cornea was then mounted in the movable container containing a preheated saline solution. On the container were attached optically flat windows where the laser light beam and the scattered light could enter and exit.

Ordinarily both corneas from a rabbit were mounted in holders and placed in the same container. One of the corneas acted as a reference cornea. With a

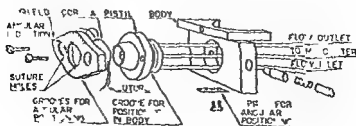


Fig 6

Part diagram of the cornea holder. The material is acrylic plastic.

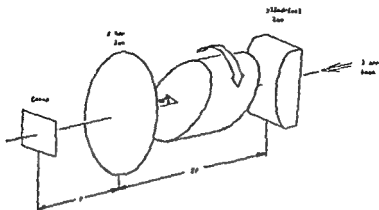


Fig 4

The coherence spoiler which through rotation of the thick piece of glass changes the angle of incidence of the light beam on the cornea

difficulty was bypassed by changing the angle of incidence of the illuminating beam in time. If the change of angle is sufficiently fast a slow detector will observe an essentially incoherent beam and the fluctuations in the detector output will be much smaller than when the angle of incidence is constant. An arrangement as shown in Fig 4 will act as a coherence spoiler by shifting the laser beam in angle but keeping the focal point stationary. The shift of angle is about 6 mrad.

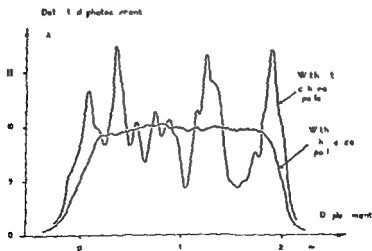


Fig 5

The figure shows a run on an opalescent piece of glass instead of a cornea with and without coherence spoiler. The interference peaks disappear when the coherence spoiler is active.

The rotating glass plate will produce a 9% intensity modulation of the laser beam when it is linearly polarized. In applications where these periodic losses are disturbing one can either use circular polarization antireflection coatings or a thicker plate at smaller angle to the beam. In Fig 5 is shown a recording from a circular opalescent glass plate with and without coherence spoiler. An improvement in signal to noise ratio of more than 10 is observed. With the rotating beam technique the signal to noise ratio in the signal recorded from the scattered light from the cornea is about 50.

The phase sensitive detector used for measuring the current from the photomultiplier requires a chopped light beam and a reference signal with a frequency identical to or at a harmonic of the chopper frequency. The light beam from the laser was chopped using an ordinary chopper wheel driven by a small synchronous motor. The generator driving the motor also supplies the reference signal to the phase sensitive detector. The chopper frequency was chosen to be 1.3 Hz.

The laser output power was monitored on an oscilloscope using a second photomultiplier as a detector. An uncoated optical flat deflects part of the laser beam onto the cathode of this photomultiplier. The laser was always allowed to stabilize its output power for at least one hour after it had been switched on before any measurements started.

The excised corneas were mounted in a special holder see Fig 6. The holder allows the intraocular pressure to be varied while at the same time a nutrition solution (TC 199) could slowly pass by the endothelial part of the cornea. The holder with the cornea was then mounted in the movable container containing a preheated saline solution. On the container were attached optically flat windows where the laser light beam and the scattered light could enter and exit.

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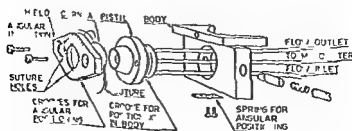


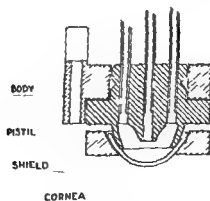
Fig 6
Part diagram of the cornea holder. The material is acrylic plastics.

simple switch it was possible to change corners and measure the light scattering from the reference corner. Thus for instance if the intraocular pressure was raised in the measuring corner and the light scattering increased it was easy to check whether this was due to the increased pressure or to improper biological treatment of the corners. The reference corner was also used as a gauge for how long the corners could be used for measuring purposes.

The temperature in the saline solution was servo controlled to 39 C by the use of an adjustable switching thermometer and a heater element molded into the bottom of the container. Also the intraocular pressure was servo controlled using a pressure meter and a motor driven hypodermic syringe.

Treatment of the cornea

The rabbits were killed by a lethal dose of nebulal sodium and the eyes were immediately enucleated. The eye was sewed by the sclera close to the corner into a special holder with the corner pointing downwards see Fig 7. A cut was made in the sclera and the dorsal hemisphere of the eye was cut away. Even though the intraocular pressure was then zero of course the natural curvature of the cornea was kept intact. Very cautiously the lens and the vitreous humour were lifted away. A tiny radial cut was made in the iris which thereafter could be pulled away. Remaining now was the cornea and a relatively broad ring of the sclera in which the tissue was sewed to the holder. The tissue was rinsed several times with a saline solution to remove any remainders of the pigmented iris. Finally the rest of the holder was clamped on so that the scleral ring acted as a leathering. The nutrition solution at an appropriate intraocular pressure was applied. Finally the holder could be mounted in the saline container. To



Fig

The cornea is mounted with the scleral ring acting as a leathering

learn the proper way of handling the cornea and the proper mounting sequence required many experiments. In the beginning the corneas started to swell and the scattering increased rapidly almost immediately after mounting. Finally the described method worked out very well and we could not see any sign of swelling or scattering increase for the first three to four hours.

Measurements

The results presented here deal with fresh corneas with one exception discussed below. Pilot experiments and several experiments with older corneas are discussed in Lindstrom (1963). TC 199 was used as the endothelial medium on all corneas discussed here while the epithelial medium in most experiments was 0.9% NaCl solution.

In a few cases silicone oils with viscosities of 0.65 cst and 50 cst were tried since the corneas were supposed to be inert regarding this substance. However, our experience is that this is not true as we found an apparent dehydration of the corneas in these experiments.

A typical registration with two superimposed consecutive runs of scattered light intensity versus corneal depth at 14 mmHg intraocular pressure (IOP) is shown in Fig. 8. The reproducibility of even small scatter peaks confirms the good resolution of the measuring system.

The curve of Fig. 8 can be divided into three interesting regions. Region a

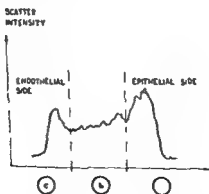


Fig. 8

The figure shows two consecutive runs on one cornea with an intraocular pressure of 14 mmHg applied. As can be judged from the picture the reproducibility of the scatter peaks is very good, showing that even the small peaks are real and not due to artefacts.

the epithelial side normally shows the strongest scatter peak. The scatter from region b the stromal part is irregular and of lower intensity than in a and c whereas region c consists of the endothelial peak normally of lower intensity than the epithelial peak. The total thickness of the cornea can be calculated from the curves taking into consideration the scanning velocity and the scattering angle. However here we considered it of minor importance to calibrate the axis since the aim is to investigate the general characteristics of the scattered light from different corneal regions.

As long as IOP is well below 70 mmHg the endothelial membrane is supposed to maintain the pressure balance in the cornea. In a fresh intact cornea (≤ 3 hours after enucleation) and with moderate changes in IOP the change in scatter response due to changes in IOP is significant though small. Fig 9 illustrates the course in a typical case. Fourteen runs on one cornea with a few minutes interval between each run and with changes in IOP in steps up to 54 mmHg have been put together in this figure. The IOP has been increased from 14 mmHg to an abnormal value and then back to 14 mmHg again to see whether the changes in scatter are reversible.

As stated earlier it can be seen that significant changes occur mainly in the epithelial region. The epithelial scatter peak increases and broadens when the IOP is increased while the stromal and endothelial regions change very little. The time $t = 0$ corresponds to 45 minutes after enucleation. As the eye ages the

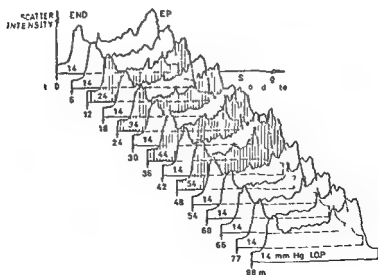


Fig 9

Fourteen runs on a fresh cornea with various IOP applied. The time $t = 0$ is 45 minutes after enucleation.

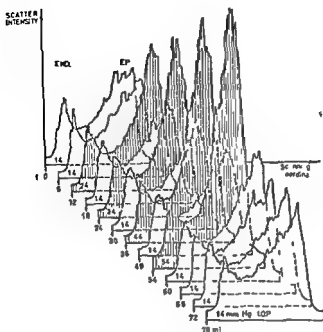


Fig 10

As in Fig 9 but with a cornea allowed to age 5 hours *in vitro* before measurements started

corneal tissue seems to lose its elasticity and becomes softer and weaker. This results in a considerably more pronounced change in scattered intensity with changes in IOP and at the same time a certain amount of hysteresis that is irreversible changes start to occur. Fig 10 shows a sequence of curves from a cornea aged about 5 hours *in vitro* before the start of the measurements.

As is clearly illustrated on Fig 10 there is an enormous increase of the scattered intensity at the epithelial side even with a moderate increase in IOP. Comparison of the first and last runs also shows an irreversible change and a broadening and increase of the epithelial scatter peak. In the stromal and endothelial regions there are however still relatively small and reversible changes.

To further illustrate the difference between Fig 9 and Fig 10 the scattered intensity from the epithelial and endothelial peaks have been constructed in Fig 11 together with a curve showing the change in corneal thickness as measured from the recordings of Fig 9 and Fig 10. Points not specifically indicated refer to 14 mmHg IOP. For the fresh cornea one can see that the scattered intensities at 14 mmHg IOP points are approximately equal showing that the

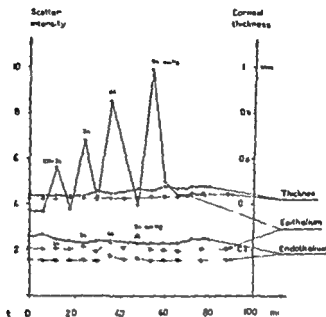


Fig 11

Measured amplitudes of the epithelial and endothelial scatter peaks from Figs 9 and 10 respectively. The corneal thickness is also monitored in the figure.

cornea undergoes reversible changes when the IOP is increased at least as can be judged from these optical measurements. There is a very small though noticeable tendency for the cornea to increase its thickness as time goes on. The thickness seems to be independent of the pressure changes.

For the old cornea the changes are more drastic. Except for the large changes of epithelial scatter one notices that the scattered intensity at 14 mmHg IOP is far from constant and that the thickness increase is no longer negligible. The decrease in thickness at some points is probably an artefact due to a motion of the cornea opposite to the scanning direction of the detector. This is also an indication of deteriorating elasticity.

From the very large material gathered in the measurements a number of interesting calculations can be performed. For instance it is possible to make a rough estimate of the magnitude of the time constant for rebalancing the tissue after a change in IOP. If we define the time constant τ as the time it takes for the scattered intensity to reach 1/e of the final value we find $\tau \approx 10$ minutes.

In a few experiments we made a sudden change in the tonicity of the nutrition solution at the endothelial side to see how this would affect the distribution of scattered intensity in the cornea. Fig 12 shows a measurement where the

Corneal Light Scatter

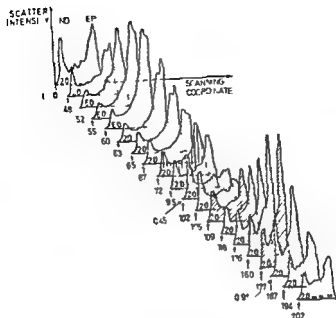


Fig 1

Samples of runs on a cornea subjected to changed tonicity in the endothelial fluid at $t = 10$ and $t = 157$ minutes from start $t = 0$ is approximately 45 minutes from enucleation

cornea has been subjected to a pressure increase to 60 mmHg IOP for about 70 minutes after a normal run at 20 mmHg IOP. After that the IOP was decreased back to 20 mmHg IOP and the conditions were allowed to re-stabilize. Then the osmotic pressure of the perfusing liquid was decreased by changing the saline concentration from 0.9% to 0.45%.

The figure shows that the changed osmotic conditions decrease the epithelial and increase the endothelial scattered intensity at first. After about seven minutes the extreme values are reached. The reverse course starts together with a significant decrease in corneal thickness. The effect is also illustrated in Fig 19 showing the maximum scattered intensity at the endothelial and epithelial side as well as the corneal thickness versus time.

After a normalizing of the osmotic conditions the thickness as well as the scattered intensity come back to their original values with a time constant of approximately 9-10 minutes.

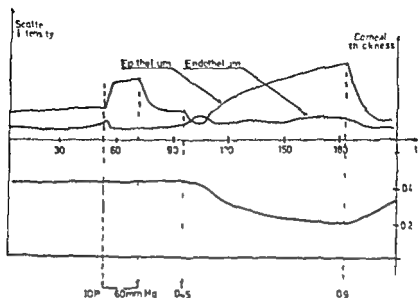


Fig 13

Measured amplitudes of epithelial and endothelial scatter peaks from Fig 12 together with a curve showing the changes of corneal thickness

Conclusions

From the results presented it is evident that the main contribution to the integrated scattered intensity from the cornea comes from regions close to the limiting layers, i.e. the epithelium and endothelium. It has been verified that the increase of the scattered intensity accompanying an increase of the intraocular pressure comes mainly from the anterior part of the cornea. This result is consistent with the theories by Berkley (1969) and by Feuk (1970) regarding the mechanical structure and the fibril distribution in the corneal stroma respectively. An investigation of the time required to rebalance the proper pressure as well as osmotic conditions in the cornea shows that in both cases a time constant of about 10 minutes can be regarded as a first estimate. A knowledge and understanding of these time constants is of great value for proper drug administration and for better understanding of the "pumping mechanism" in the endothelial membrane. It is suggested that further investigation regarding the membrane properties and the forces required to keep the stromal fibrils in their proper positions be carried out.

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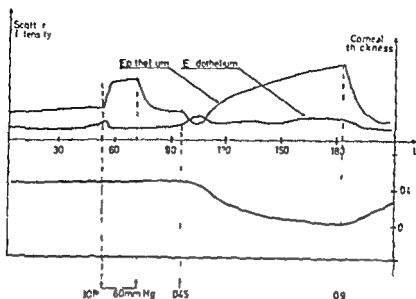


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FLUOREXON VITAL STAINING OF CORNEA AND CONJUNCTIVA

BY

M S NORN

Fluorexon is a large molecular fluorescein derivative which may be of use in the fitting of soft contact lenses

Its staining properties have been assessed by slit lamp examination of 146 eyes and microscopy of 40 preparations

The dye effected partly fluorescent and partly nonfluorescent staining. Both components were best seen in cobalt filtered light. The fluorescent component was noticed in the presence of epithelial defects corresponding to the conditions seen after staining with fluorescein though of a much lower grade. The non fluorescent component represented staining of dead or degenerate cells thus having the same properties as rose bengal though likewise staining less intensely.

Using fluorexon instead of fluorescein and rose bengal will obscure in formation concerning various important facts (punctate fluorescein staining epithelial blebs epithelial defect of dendritic pattern mild kerato conjunctivitis sicca etc.)

Key words: cornea - conjunctiva - vital staining - fluorexon - fluorescein - rose bengal - contact lenses - soft contact lenses

It is a well known fact that one must be wary of vital staining with fluorescein in connection with fitting of soft contact lenses. There ought to be an interval of from one to several hours between vital staining and insertion of a soft lens in order to avoid permanent discoloration of the lens.

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Refojo et al (1972) introduced a larger fluorescein containing molecule for vital staining to prevent penetration of the fluorescein through the porous structure of the lens. This compound is named fluorexon. Its molecular weight of 710 (that of fluorescein 376) should generally prevent its penetration of Bausch & Lomb's soft lens for instance.

Fluorexon has hitherto been employed for calcium titration in the laboratory. Its formula is bis (N N bis(carboxymethyl aminoethyl) - fluorescein tetrasodium salt.

Refojo et al used the compound to assess the clearance of the soft lens before blinking a procedure which allegedly gives a rough estimate of the curvature of the lens in proportion to that of the cornea concerned.

The object of the present study was to evaluate the properties of fluorexon as a vital stain of cornea and conjunctiva particularly as compared with those of fluorescein.

Present Investigations

Fluorexon is a yellow water soluble substance. It causes no smarting pain when instilled into the eye. No side effects were noticed during the present study and in particular no permanent staining (tattooing) occurred. Slit lamp examinations were done on 146 eyes and 40 preparations were studied under the microscope. The series comprised patients from the Eye Department and the Ophthalmic Out Patient Department *Kommunehospitalet* and patients from the author's practice (Vanløse).

One drop (0.01 ml) of 2% vital stain was instilled into the inferior fornix. The staining was estimated in the slit lamp when after blinking excess dye had been washed away with the tear fluid.

Microscopy

The mucous thread in the inferior fornix (Born 1973) was vital stained by fluorexon. The mucous thread was transferred from the inferior fornix to a slide by means of two wooden sticks. When these had touched the medial and the lateral ends respectively the thread was carefully detached from the conjunctiva and carried between the two sticks to the slide. One drop of saline

was added and a cover slip was laid over. The vital stained mucous thread was now ready for microscopy.

Vital staining with 2% fluorexon gave a beautiful yellowish orange coloring of the mucous thread constituents. The cells were the most intensely stained elements, the nuclei more so than the cytoplasm and granules. All cell species were found to be stainable (leukocytes, epithelial cells of all kinds). Some cells had a fairly pale color and even unstained cells of any species were seen scattered about.

The mucous thread fibrils were generally less intensely stained than the cells. Vacuoles remained unstained.

Under subsequent staining with 1% rose bengal all yellow cells became red i.e. stained by rose bengal.

Vital staining with 1% trypan blue either subsequently or in a mixture with fluorexon gave predominantly blue cells with a small percentage of yellow cells in between. This suggests that fluorexon stains not only dead cells (stained by trypan blue Norm 1967) but also some degenerate cells.

Vital staining with 1% alcian blue and fluorexon gave a useful double staining. mucus assumed a bluish green color and cells a yellowish orange.

Vital staining with *fluorescein* yielded a picture differing completely from that with fluorexon. Using 1% or 10% fluorescein we got unstained cells with a diffusely stained yellow background. Slightly stained cells were seen in rare cases only. The fluorescein dye enclosed the mucous thread and diffused into the surrounding saline. Fluorescein staining of the mucous thread must be regarded as a false staining. Actually the mucous thread is merely enclosed by the dye solution owing to capillary forces of attraction.

Vital staining with fluorexon on the other hand is a true staining. Fluorexon penetrates into the cells and stains the nuclei more than the cytoplasm. The mucous thread is not surrounded by diffusing dye. No dye is given off to the surroundings by pressure on the mucous thread.

Slit Lamp Examination

The main object of the present investigation was to draw a comparison between vital staining with fluorexon and vital staining with fluorescein. Fluorexon was instilled first and the result read in the slit lamp was entered in a diagram stating the staining grade. The staining was graduated arbitrarily from 1 to 5 indicating moderate staining, 2 weak, 4 intense, 1 minimum and 5 maximum.

Table 1

The clinical series vital stained by 2% fluorexon and 1/8% fluorescein. Others comprise herpetic keratitis, graft bullous keratitis, simple conjunctivitis, iritis, glaucoma, pterygium, exophthalmos, subconjunctival hemorrhage, follicular conjunctivitis, episcleritis.

Normal	54
Erosion/corrosion	14
Dendritic keratitis	7
Marginal keratitis	8
Central keratitis	4
Contact lens	5
Keratoconjunctivitis sicca	9
Infectious conjunctivitis	4
Cataract extraction	7
Others	23
Total	120

Then followed instillation of fluorescein with a corresponding reading of the result.

Which concentration is appropriate?

0.4% fluorexon is equimolar with 0.25% fluorescein. Fluorexon is however less fluorescent at this concentration than fluorescein because no linear increase of the fluorescence occurs at rising concentrations (Refojo et al. 1972).

Initially I employed 1/4% fluorexon and 1/8% fluorescein. In the main series the concentrations used were 2% fluorexon and 1/8% fluorescein. At this concentration fluorexon had optimum conditions against the weak fluorescein solution.

The initial series comprised 26 eyes and the main series 120 eyes. The clinical diagnoses of the main series are shown in Table 1. Subsequent staining was undertaken with 1% rose bengal in 26 cases and with 1% trypan blue in 8.

The first vital stainings immediately showed fluorexon to stain in two different ways: some areas displayed marked yellow fluorescence when illuminated by cobalt filtered light, while others were brownish black, non fluorescent in cobalt filtered light and yellow in white light. The latter were also most distinct in cobalt filtered light.

Below the fluorexon component giving fluorescent areas will be named F\XON and that giving non fluorescent areas N\XON.

was added and a cover slip was laid over. The vital stained mucous thread was now ready for microscopy.

Vital staining with 2% fluorexon gave a beautiful yellowish orange coloring of the mucous thread constituents. The cells were the most intensely stained elements, the nuclei more so than the cytoplasm and granules. All cell species were found to be stainable (leukocytes, epithelial cells of all kinds). Some cells had a fairly pale color and even unstained cells of any species were seen scattered about.

The mucous thread fibrils were generally less intensely stained than the cells. Vacuoles remained unstained.

Under subsequent staining with 1% rose bengal all yellow cells became red i.e. stained by rose bengal.

Vital staining with 1% trypan blue either subsequently or in a mixture with fluorexon gave predominantly blue cells with a small percentage of yellow cells in between. This suggests that fluorexon stains not only dead cells (stained by trypan blue, Norn 1967) but also some degenerate cells.

Vital staining with 1% alcian blue and fluorexon gave a useful double staining: mucus assumed a bluish green color and cells a yellowish orange.

Vital staining with *fluorescein* yielded a picture differing completely from that with fluorexon. Using 1% or 10% fluorescein we got unstained cells with a diffusely stained yellow background. Slightly stained cells were seen in rare cases only. The fluorescein dye enclosed the mucous thread and diffused into the surrounding saline. Fluorescein staining of the mucous thread must be regarded as a false staining. Actually the mucous thread is merely enclosed by the dye solution owing to capillary forces of attraction.

Vital staining with fluorexon on the other hand is a true staining. Fluorexon penetrates into the cells and stains the nuclei more than the cytoplasm. The mucous thread is not surrounded by diffusing dye. No dye is given off to the surroundings by pressure on the mucous thread.

Slit Lamp Examination

The main object of the present investigation was to draw a comparison between vital staining with fluorexon and vital staining with fluorescein. Fluorexon was instilled first and the result read in the slit lamp was entered in a diagram stating the staining grade. The staining was graduated arbitrarily from 1 to 5, 3 indicating moderate staining, 2 weak, 4 intense, 1 minimum and 5 maximum.

Table II

Staining of cornea and different conjunctival areas 2% fluorescent fluorexon (F\ON) 1/8% fluorescein (FLU) and non fluorescent fluorexon (N\ON) The figures indicate in per cent the number stained at the site concerned

	F\ON	FLU	N\ON
Cornea	20.8	44.2	21.7
Bulbar conj	4.2	14.2	15.0
Plica semilunaris	5.8	18.3	11.7
Caruncle	95.0	47.5	19.2
Inferior fornix	0	2.5	0
Inferior tarsus	6.7	17.5	6.7
Marg. line	7.5	16.7	71.7

Normal Eyes

In six out of 34 normal eyes micropunctate fluorescein staining was seen scattered over the cornea. Such staining noticed in elderly individuals was found in four patients aged 80 years old one aged 70 and one aged 60 (cf Norm 197). Neither F\ON nor N\ON gave a similar punctate staining which did not appear till the subsequent fluorescein staining.

F\ON may occasionally give punctate staining of the tarsus along the line at right angles to the lid margin exactly like fluorescein.

Pathological Cases

In cases of extensive corneal erosion the lesion was stained by F\ON though with a weaker fluorescence than caused by fluorescein. As when staining with fluorescein the lesion itself could be observed to be stained immediately then to spread within a few minutes round the lesion the dye diffusing into the intercellular spaces between the surrounding normal epithelial cells.

Minor corneal erosions were stained by fluorescein but not by \ON.

Pronounced corruptions by sodium hydroxide were stained intensely by fluorescein and less so by F\ON. The border of the corruption was stained weakly by N\ON.

Of the dendritic keratitis cases three were stained by F\ON five by N\ON and all seven by fluorescein.

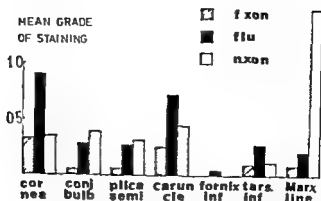


Fig 1

Mean staining grade on cornea and different conjunctival areas. Arbitrary grading 1 to 5. Fluorescent fluorexon (F \ ON), fluorescein (FLU) and non fluorescent fluorexon (N \ ON). 120 eyes.

Location

Fig 1 illustrates the results with regard to the main series. F \ ON is seen to have given much less fluorescence than fluorescein; the mean fluorescence grade being about three times higher with fluorescein than with F \ ON.

Further, the proportions are seen to have been approximately the same in all the regions examined (cornea, bulbar conjunctiva, plica semilunaris, caruncle, inferior fornix, inferior tarsus, and Marx line along the lower lid margin). In other words, F \ ON stains in the same manner as fluorescein, but the staining grade is much lower.

As for N \ ON, the staining was seen to be distributed in a totally different manner; this component staining Marx line very intensely, and the bulbar conjunctiva and caruncle fairly intensely. The distribution over the various sites corresponds closely to that of rose bengal (cf Norn 1967, Figs 2A and 2B). However, N \ ON staining is of a considerably lower grade than rose bengal staining (Marx line in this series showed a mean grade of 1.5 with N \ ON against about 3 with rose bengal in two other series, Norn 1967).

Table II shows the results of vital staining in the different regions, stated in percent. F \ ON is seen to have stained in no more than about half of the cases stained by fluorescein. Marx line was often stained by N \ ON, whereas it was rarely stained by F \ ON, and fluorescein. Marx line was stained by N \ ON in 72 per cent (by rose bengal in practically 100 per cent, Norn 1972).

Table II.

Staining of cornea and different conjunctival areas 2% fluorescent fluorescein (FL) and non fluorescent fluorescein (FNON). The values indicate, in per cent, the number stained at the site concerned.

	FNON	FL	NON
Cornea	29.9	44	21
Bulbar conj	4	14.2	15.3
Plica semilunaris	3	13.3	11
Caruncle	3.3	4.5	13
Inferior fornix	0	2	1
Inferior tarsus	6	17.5	6
Marx line	7.5	15	7

Normal Eyes

1 out of 14 normal eyes micropunctate fluorescein staining, was seen scattered over the cornea. Such staining noticed in elderly individuals was found in first patient aged 99 years old, one aged 88 and one aged 80 of Norway. Neither FNON nor NON gave a similar punctate staining which did not appear till the subsequent fluorescein staining.

FNON may occasionally give punctate staining of the tarsus along the line of contact to the lid margin exactly like fluorescein.

Pathological Cases

In cases of extensive corneal erosion the lesion was stained by FNON though with a weaker fluorescence than caused by fluorescein. As when staining with fluorescein the lesion itself could be observed to be stained immediately then to spread within a few minutes round the lesion, the dye diffusing into the intercellular spaces between the surrounding normal epithelial cells.

Most corneal erosions were stained by fluorescein, but not by NON. Pronounced erosions by sodium hydroxide were stained intensely by fluorescein and less so by FNON. The border of the corrosion was stained weakly by NON.

Of the dendritic keratitis cases three were stained by FNON five by NON and all seven by fluorescein.

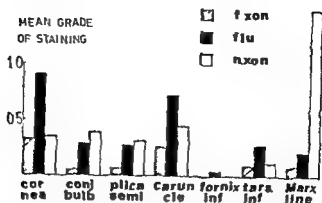


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Fluorexon Vital Staining

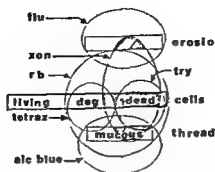


Fig 2

Fluorexon vital staining The diagram shows the structures vital stained by fluorexon (XON) fluorescein (FLU) rose bengal (RB) isodonitrotetrazolium (TETRAZ) alcian blue (ALCBLUE) and trypan blue (TRY) The dyes are symbolized by circles and ovals and the structures (mucous thread cells and erosion) by quadrangles The fluorexon stained structures are hatched

The present investigation also showed however that the larger molecule yields additional vital staining properties which make the dye differ essentially from fluorescein

Both forms can be witnessed after staining of a fairly deep erosion by fluorexon the bottom of the erosion becomes fluorescent and the fluorescence diffuses around the erosion (F \XON) At the same time there is found a yellow non fluorescent region along the border (N \XON) where no diffusion takes place

The F \XON staining property corresponds to that of fluorescein The dye stains epithelial defects and may diffuse through suitably large cell interspaces By comparing F \XON with fluorescein in the clinical series we found that the same regions (Fig 1) and the same clinical states were stained by both dyes though much more intensely by fluorescein than by fluorexon

The \XON staining property differs completely from that of fluorescein The dye stains degenerate and dead epithelial cells It does not diffuse into the surrounding tissue Unlike fluorescein \XON stains Marx line frequently and intensely (Fig 1) Its staining property corresponds to that of rose bengal but the latter dye stains more intensely

Fluorexon is thus an interesting dye which has the staining properties of both fluorescein and rose bengal combined in one single molecule

Fig 3 illustrates the staining properties of fluorexon compared with those of other known vital stains

Of the *marginal keratitis* cases two presented an epithelial lesion which was stained by fluorescein but not by F \ ON

In *central keratitis* the central process was stained to satisfaction by F \ ON while diffuse punctate elements were stained exclusively by fluorescein

In cases of corneal lesions with small *blebs* these were definitely disclosed as small holes in the fluorescein stained precorneal film Such holes were difficult or impossible to recognize in the F \ ON stained precorneal film Similarly Schweitzer's pattern is easy to study when using fluorescein but difficult when using F \ ON

In *keratoconjunctivitis sicca* the corner and the exposed portion of the bulbar conjunctiva were stained the most intensely by rose bengal more weakly by N \ ON and poorly by fluorescein and I \ ON In five out of nine cases N \ ON staining failed on the cornea despite characteristic rose bengal staining

A contact lens that was too steep caused pathological fluorescein staining but no I \ ON staining

A crescentic rose bengal stained area of the bulbar conjunctiva due to pressure by the lower edge of a lens was only weakly stained by N \ ON

Such *micropunctate staining* as seen in different morbid conditions in response to *fluorescein* (after cataract extraction in glaucoma in episcleritis) could not be brought about by F \ ON nor by N \ ON (nine cases)

Summarizing we may say that the following disorders would fail to be diagnosed if 2% \ ON were used instead of 1/4% fluorescein micropunctate fluorescein stained defects small corneal blebs minor erosions fairly mild dendritic keratitis contact lens provoked affection of the corner

A diagnosis of keratoconjunctivitis sicca may be missed by using \ ON instead of rose bengal

A comparison of the initial series with the main series showed 1/4% \ ON to stain more weakly than 2% \ ON

Subsequent staining with rose bengal showed this to stain more frequently and more intensely than N \ ON in all regions

DISCUSSION

Fluorexon has a molecule twice as large as that of fluorescein This probably accounts for the observed non staining by fluorexon of micropunctate corneal defects which only become visible after staining with fluorescein Larger defects become stained by fluorexon though less intensely so than by fluorescein

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PACHOMETRIC STUDY ON THE INFLUENCE OF CORNEAL ENDOTHELIAL VITAL STAINING

Corneal Thickness after Cataract Extraction Studied by Vital Staining with Trypan Blue

BY

M. S. NORN

The corneal thickness was measured in 114 cases prior to cataract extraction. On the second postoperative day a 15 per cent increase of the thickness was noticed, and on the sixth postoperative day a 9 per cent increase. At a follow up 6 to 12 months later the thickness was as before the operation. Half of the eyes were vital stained during the operation by filling the anterior chamber with 0.1% trypan blue. Such staining has no harmful effect on the corneal endothelium, assessed by the corneal thickness and by occurrence of corneal epithelium oedema.

Key words: corneal thickness - corneal endothelium - vital staining - trypan blue - pachometry - cataract extraction

The corneal endothelium can be vital stained in vivo. I have previously published a report (Norn 1971) on staining with trypan blue or with a mixture of rose bengal and fluorescein. The vital staining was performed during cataract extraction. Such vital staining seemed to have no side effects.

The diagram shows that fluorexon stains dead cells a small number of degenerate cells and slightly stains mucus (N\ON) and intercellular matter (F\ON). In the diagram we find rose bengal, trypan blue (staining dead cells), alcian blue (mucus) and tetrazolium (enzyme containing degenerate cells).

Fluorexon has the advantage of being useful in connection with a soft contact lens. However, in clearance studies prior to blinking there is hardly any need for it, partly because other methods are available for assessing the fitting of a soft lens and partly because the lens should settle down for 20–30 minutes before its fitting can be assessed. Finally, a soft contact lens may possibly in rare cases become discolored by fluorexon after all (Davies 1973).

It is tempting to use fluorexon for studying possible lesions or traces of pressure on cornea and conjunctiva in relation to wearing of a soft contact lens. With this dye it is not necessary to wait at least a full hour before the lens can be reinserted, as is required in the case of fluorescein.

The objection may be raised, however, that by using fluorexon one runs a risk of missing important facts, such as minor erosions, micropunctate defects and traces of pressure. The optimum technique of vital staining must therefore still be based on use of fluorescein or even better a mixture of 1% fluorescein and 1% rose bengal. This means, however, that the soft contact lens cannot be reinserted until all vital stain has disappeared.

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Cataract extraction was performed with limbus based conjunctival lobe two preplaced 8-0 silk sutures chamber opening with knife corneoscleral cutting with scissors basal iridectomy removal of lens with cryo extractor three post placed 8-0 knotted silk sutures and continuous silk sutures in the conjunctiva Only patients aged under 60 were given a chymotrypsin Dehydrating treatment (glycerin - 0.67 g/kg by mouth for 1½ hours pre operatively) was given only to patients under 60

All the operations except seven (out of 114 cataract extractions) were performed by the author The remaining seven were also performed by experienced ophthalmic surgeons

The vital staining was undertaken during the cataract extraction After cutting the chamber was filled with 0.1% trypan blue from a syringe mounted with a small blunt lacrimal passage needle - prior to cryo extraction of the lens

Material

The series studied comprised all the patients admitted consecutively for cataract extraction on the author's days on duty in the operating room a total of 114 patients admitted within one month were subjected to vital staining with

Table 1
Composition of the material surgical technique and complications

	Vital stained	Control series
initial corneal thickness (mm)	0.524	0.515
mean age (years)	19	75.0
extracapsular operation	3	0
corneal incision	0	1
chymotrypsin	6	3
loss of vitreous	6	3
iris prolapse	0	3
vitreous - cornea contact	3	4
vitreous > ½ chamber	12	8
hem in chamber > ½	3	1
ten on bed	3	1
Total	5	5

In 84 per cent the staining disclosed endothelial injuries manifesting themselves as transverse lines at the sites of curving of the cornea during cataract extraction. In some cases lesions were also seen caused by touch of a needle (used for injecting chymotrypsin). The vital staining might be an aid in estimating the chamber depth and for exact wound adaptation.

Clinical examinations of 99 cataract extracted eyes subjected to endothelial vital staining, and 88 cataract extracted control eyes revealed no clinical signs of endothelial damage due to vital staining (Norn 1971).

The corneal endothelium is well known to have the important function of keeping the cornea dehydrated (the endothelial pump). When the endothelium is damaged the cornea will become thicker. When measured with a modern apparatus alterations of the corneal thickness represent an exact parameter of the endothelial vitality. The object of the present investigation was to subject the vitality of the corneal endothelium to a pachometric study after staining *in vivo* as suggested by C. Dohlman (1971).

Method

The corneal thickness was measured in a Haag Streit slit lamp 900 mounted with Haag Streit's pachometer. The thickness was measured three times with three different adjustments. The mean value was employed.

Most of the patients could fix the light beam to satisfaction – also before the operation. In the cases with fixation troubles it was necessary to employ fixation light in front of the contralateral eye. The correct adjustment was controlled directly through the slit. All measurements were carried out by the author.

The pachometric measurements were not corrected for the corneal curvature primarily because we were solely interested in the percentage alterations of the corneal thickness.

The corneal thickness was measured the day before the operation, two days after the cataract extraction, six days postoperatively, and finally 8 to 12 months after the operation. Four groups of patients were summoned at intervals of six months to be able to carry through this latter part of the investigation.

Following pachometry the patient was examined in the slit lamp for corneal epithelial oedema, blebs, and other complications. The eyes were examined for incipient oedema by sclerotic scatter, without and with magnification. (A broad slit lamp light beam focused on the area of transition from sclera to cornea will disclose even the slightest oedema as a white diffuse opacity, best seen with the naked eye.)

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Corneal Endothelial Vital Staining

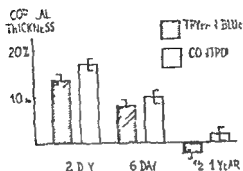


Fig 1

Corneal thickness after endothelial vital staining with 0.1% trypan blue Abscissa interval after cataract extraction Ordinate percentage increase of thickness compared with pre operative measurement

Table III illustrates the result of the preoperative endothelial vital staining. The endothelium was stained in 41 out of 51 cases. The figures of the table indicate the percentage increase of the corneal thickness. This increase seemed to be independent of the stainability of the endothelium. The corneal thickness increased even in cases where trypan blue did not stain the endothelium.

The corneal epithelium was often seen to be oedematous on the second post operative day, whereas less frequently so on the sixth. Pronounced oedema was seen in four cases on the second postoperative day and in four on the sixth. Mild oedema in some instances only recognizable by sclerotic scatter was present in 4 cases on the second postoperative day and in 13 on the sixth. Minor blebs were found in five on the second day against only one on the sixth.

Table III

Stainability of endothelium compared with percentage increase of corneal thickness after cataract extraction

Stainability of endothelium	2nd day	6th day	6-1 months	Number
Stained	130	45	100	10
Not stained	15	100	10	15
Total	145	145	110	25

0.1% trypan blue while patients admitted within the next month acted as controls. The two groups comprised 57 patients each.

At the follow up 6 to 12 months later 85 per cent (47 vital stained and 50 controls) were examined. 17 patients could not be followed up owing to death, change of address or failure to appear for different reasons.

Table I shows the composition of the material, surgical technique and complications. It is evident that the vital stained series is comparable with the control series.

Result

The corneal thickness prior to the operation was 0.524 mm in the series vital stained during the operation and 0.515 mm in the control series or approximately the same as that stated for normal series described in the literature (Mishima et al 1968; Ehlers et al 1971; Kruse-Hansen 1971). The values have not been corrected for corneal radius nor for preferential use of one eye.

The results of the investigation are shown in Table II and in Fig. 1. The corneal thickness is seen to have increased by about 15 per cent on the second postoperative day. On the sixth postoperative day the thickness had decreased to about 8–10 per cent above normal. The decrease from the second to the sixth day is significant. At the follow up 6 to 12 months later the cornea had attained the pre-operative thickness.

No significant difference was noticed between the vital stained and the control series either on examination the second and the sixth day or at the follow up 6 to 12 months after the cataract extraction.

We may conclude from this that vital staining of the corneal endothelium with 0.1% trypan blue does not interfere with its function as assessed by measuring the corneal thickness.

Table II

Trypan blue staining of endothelium in relation to cataract extraction. Alteration of corneal thickness in per cent

	2nd day	6th day	6–12 months
trypan blue	13.6 ± 1.5	8.0 ± 1.4	-2.3 ± 1.3
controls	11.0 ± 1.3	9.9 ± 1.4	+1.5 ± 1.4

Corneal Endothelial Vital Staining

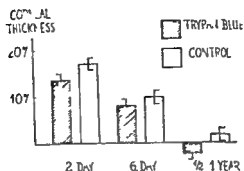


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Table III

Stainability of endothelium compared with percentage increase of corneal thickness after cataract extraction

Art. to be graded	1 day	6th day	6-1 months	Number
Staining endoth.	15.0	4%	10.0	10
"	15	10.0	1.0	15
"	1	5.1	2.0	16
" 4	15.0	9.5	3	10

0.1% trypan blue while patients admitted within the next month acted as controls. The two groups comprised 57 patients each.

At the follow up 6 to 12 months later 85 per cent (47 vital stained and 50 controls) were examined. 17 patients could not be followed up owing to death, change of address or failure to appear for different reasons.

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trypan blue	13.6 ± 1.5	5.0 ± 1.4	-2.8 ± 1.3
controls	14.0 ± 1.3	9.9 ± 1.4	$+1.5 \pm 1.4$

series under review (about 15 per cent on the second day and 22 per cent on the sixth)

The discrepancy may be accountable for by different surgical techniques Giardini used Graefe's knife Arruga tweezers or crysiphake and only two sutures Giardini found the corneal thickness to have returned to normal about the 36th day

Dohlman and Miller measured 30 consecutive cases of unilateral aphakia more than six months after the operation In 76 per cent they found the cornea to be thicker in the aphakic eye than in the normal They concluded that in many cases increased corneal thickness will persist beyond six months

This result was in disagreement with that arrived at by Giardini and that of the present investigation where the corneal thickness seemed to have been normalized within six months

The corneal thickness is in the first place a function of the vitality of the endothelium which latter pumps sodium out of the cornea into the aqueous humour

The present investigation showed that preoperative vital staining with trypan blue during cataract extraction does not damage the corneal endothelium so much that the corneal thickness increases

The vital staining disclosed endothelial injuries manifesting themselves as trypan blue stained lines due to curving of the cornea and lesions caused by a needle introduced into the chamber These lesions were so small that intensified trypan blue staining effected no increase of the corneal thickness

Other factors must be supposed to have a greater share in the endothelial damage and the consequent increase of the corneal thickness Among these are peripheral endothelial damage in relation to cutting of the cornea an action of secondary aqueous humour on the endothelium blood in the chamber vitreous body contact etc Finally the intraocular pressure has an influence on the corneal thickness and the development of epithelial oedema

The staining technique employed was seen not to damage the corneal endothelium It is therefore tempting to try the method on the donor graft prior to cornea transplantation However in this situation the endothelium is most often additionally damaged The dye may possibly also penetrate from the side through the connective tissue

Cataract extraction and cornea transplantation are two different surgical interventions which hardly are fully comparable with regard to vital staining of the endothelium

At the follow up 6 to 12 months later epithelial oedema was present in only five patients in the form of odd blebs

Table IV shows that the vital stained and the control series presented no difference with regard to presence of epithelial oedema

Eyes with epithelial oedema had a thicker corneal parenchyma than eyes with no such oedema In the epithelial oedema series the corneal thickness had increased by 19.3 per cent in the vital stained series and by 20.0 per cent in the control series on the second postoperative day On the sixth postoperative day the corresponding figures were 14.8 and 18.1 per cent respectively

These figures are considerably higher than those for the total series The difference is significant

On the other hand no definite correlation was noticeable in the individual cases between the corneal thickness and presence of corneal oedema Eyes were seen presenting a greatly increased corneal thickness (> 30 per cent) but no epithelial oedema and eyes having a normal corneal thickness combined with marked epithelial oedema

Discussion

The above investigation showed that the corneal thickness increases considerably after cataract extraction

Giardini et al followed 37 cataract extracted patients They found the corneal thickness to have increased by an average of 45 per cent on the third postoperative day with a fall to an average of 20 per cent above normal on the tenth postoperative day These figures greatly exceed those found in the

Table II

Epithelial oedema and delayed complications after cataract extraction in endothelium stained and 51 controls

	Vital stained	Control series
epithelial oedema 2nd day	18	15
epithelial oedema 6th day	9	9
epithelial oedema 6-12 months	2	3
conjunctival bleb 6-12 months	3	5
vitreous prolapse 6-12 months	1	4

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ULTRAVIOLET DISINFECTION OF APPLANATION TONOMETER PRISM

BY

M S NORN

Five Goldmann tonometers have been used clinically over a two year period. They have been exposed to continuous ultraviolet light during working hours in five sterilizers constructed by us. The distance between burner and prism base is 10 cm.

The tonometer prism will last for 6 months or about 1000 hours of effective disinfection of the prism base.

Key words: ultraviolet light sterilisation - disinfection - Goldmann's applanation prism - bacteria - virus

There is still some doubt as to the most reliable and practical procedure of sterilizing Goldmann's tonometer prism.

Many methods have been suggested but only few have been controlled microbiologically.

The manufacturer of the applanation prisms (Haag Streit, Bern) recommends cleaning with cotton moistened in merphenyl 1:32 000 (phenylmercuric borate).

Such cleansing is however inadequate. Examinations of 150 merphenyl

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The prism cannot be rendered useful again by grinding the base as this would alter the weight and diameter of the prism

Each prism costs about 120 Danish kroner

Method

In the Out Patient Eye Clinic Kommunchospitalet we have used five disinfection units constructed by us. Each of these consists of a Hanau Hg low pressure burner Nk 4/4 25 W having a burning time of 6000 hours.

The burner is kept in a metal box (20 x 21 x 15 cm) with a concave mirror behind the lamp which focuses the light on the anterior surface of the applanation prism (Fig. 2).

The distance from the ultraviolet burner to the anterior prism surface is 10 cm. The apparatus has been produced by Bent Hansen Engineer Messrs Sørensen & Hald Naverland 15 2600 Glostrup Denmark Construction No 1957.

The applanation tonometer with mounted prism is passed on to a slide at the front of the apparatus placed so as to allow the prism to slip into a hole in

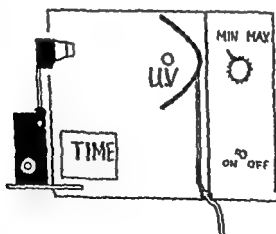


Fig.

Diagram of ultraviolet sterilizer for tonometer sterilization. C. Edmann's applanation tonometer rest on its side. The prism is irradiated by the ultraviolet Hanau burner (UV). TIME is an AFC time gauge.

treated and 100 non treated prisms employed clinically showed 70 per cent of either group to be contaminated (Norn & Frolund Thomsen)

Corboy et al found mechanical cleansing to be effective against *Staph aureus* and *Ps aeruginosa* but less so against virus (T-2 coliphagus) The cleansing was performed with cotton moistened in saline or tap water followed by drying with tissue

They recommend however cleansing of the prism for 15 minutes with a 5% aqueous formaldehyde solution after its use in cases suspected of infection

The clinic in Bern likewise recommends use of formaldehyde solution after contact with cases suspected of having infection (Schmidt)

Other methods require more equipment or a larger supply of applanation tonometer prisms (ethylene oxide gamma radiation cobalt radiation tonofilm and plates)

Several workers have employed ultraviolet irradiation of the prism base (Frolund Thomsen & Norn Dräger Lollmann Martmann Moe)

We found ultraviolet irradiation for 4 minutes to suffice for prevention of contamination However in cases suspected clinically of massive infection the prism base should be disinfected using cotton moistened in absolute alcohol prior to the irradiation (Frolund Thomsen & Norn)

Ultraviolet light has the great disadvantage of gradually damaging the prism base which crackles (Dräger Lollmann)

A system of cracks irregularities and cloudy regions will suddenly occur after a few days (Fig 1) At tonometry the two fluorescein hemispheres will be found broken and opaque The prism should be discarded not only because the reading may be unreliable but also because the cracks may harbour microbes which may have survived the sterilisation process



Fig 1

Crackled base of applanation prism damaged by ultraviolet sterilisation

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the box front. The anterior surface of the prism has thus been fixed correctly for ultraviolet irradiation (Fig. 2).

The tonometer is kept on the slide beside the slit lamp. The anterior prism surface is exposed to continuous ultraviolet light until the moment the tonometer is employed for measuring the tension.

Result

The five ultraviolet tonometer sterilizers have been in use through two calendar years (1971 and 1972). Application has been performed extensively, even in cases where infection might be suspected.

Within this period we saw no instances of accumulated epidemic keratitis (adenovirus) nor any other cases in which contamination might be attributed to application tonometry.

The sterilizers were always turned on throughout working hours (six or seven hours a day) with mounted tonometer and were employed without causing any trouble.

The prism base was wiped with alcohol at least once a day.

Nine prisms crackled within the first year and another ten within the next. In other words, an average of a scant 20 prisms were damaged in the course of two years by regular use of five sterilizers, i.e. two prisms per sterilizer each year. The prism can stand six months of constant exposure to ultraviolet light during working hours (altogether about 1000 hours).

Discussion

Dräger (personal communication) found the tonometer prism to be damaged after 200 hours of ultraviolet sterilisation with a prism-lamp distance of 1.5 cm.

The prism is more stable at a larger distance and perhaps at a lower temperature. The exposure time can be reduced in practice by fractional irradiation. However, I prefer constant light during working hours, because interruption means that the prism will not immediately be sterile and ready for use.

A distance of 10 cm between prism and lamp is kept in our apparatus, proved to give adequate disinfection (Frølund-Thomsen & Norn) and a fairly acceptable prism life, i.e. about six months at continuous use during working hours.

The purpose of the present survey is to draw the attention of the ophthalmologist to the rare and peculiar tumour pilomatrixoma. Out of a total of 19 cases collected in the Institute of Eye Pathology the correct diagnosis has not been made clinically in any case. Pilomatrixoma was first described as a benign calcifying epithelioma by Malherbe et al. in 1880. Most frequently found in young females it is a tumour originating from the skin. It can be located anywhere on the body but it appears most frequently on the neck and arms and on the face.

Material and Methods

The material collected from the Institute of Eye Pathology includes tumours from the ocular region of 19 patients during the period from 1954 to 1971. The survey was made retrospectively from the histopathological diagnosis in the card index of the Institute. All case records have been examined but often they have been found inadequate owing to the fact that the clinical diagnosis pilomatrixoma (epithelioma calcificans) was not made in any case. Most frequently the lesion was interpreted as an unspecific tumour or as an atheroma. Whether any lesions removed and not examined histologically might have been diagnosed as pilomatrixoma remains unknown.

Staining methods

Sections stained with haematoxylin and eosin were studied in each case. In certain cases special additional stains have been used, i.e. cresyl violet or haematoxylin-phloxin-saffran staining for connective tissue and reactions for disulphidyl and disulphide groups (as found in keratin). DDD reaction and alkaline tetrazolium. Staining for iron was carried out with von Kossa, alizarin red S and murexide. Ten cases were stained for melanin with Masson Fontana. In certain cases staining for citrulline (19) was attempted.

Results

Clinical data

Age and sex. One case is without any clinical information. The average age of the patients was 18 years. The youngest patient was 10 months and the eldest 75 years. The series includes seven males and eleven females. The distribution of age appears from Table 1: in two thirds of the cases the lesion occurred before the age of 30 years.

Localisation. The skin around the right eye was affected in nine cases and that around the left eye in seven. In two cases no information on side localization was available. The lesion was situated above the palpebral fissure in thirteen cases and beneath it in five cases.

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PILOMATRIXOMA

(epithelioma calcificans Malherbe)

A clinical and histopathological survey
of Danish material from 1954 to 1971

BY

JØRGEN KLEENER

A clinical and histopathological study was made in 19 cases of pilomatrixoma (epithelioma calcificans Malherbe). Clinically the analysis confirmed that pilomatrixoma is often found in young females usually above the palpebral fissure. Pilomatrixoma is a solid tumour adherent to the skin but not to the underlying tissue.

The histological picture shows epithelial strands and islands of characteristic shadow cells. The stroma is characterized by granulation tissue with foreign body giant cells. Calcifications almost always occur. The tumour is benign. Malherbe stated that the lesion was developed from the sebaceous glands but today the tumour is believed to originate from hair matrix cells. The name pilomatrixoma was therefore suggested as a better term. In none of the present cases was the correct diagnosis made clinically. In view of the difficulty in diagnosis it is emphasised that every tumour removed should be referred for histological examination.

Key words: tumours - pilomatrixoma - epithelioma calcificans - Malherbe - shadow cell

Histopathology

Macroscopic The lesion was usually 5-10 mm in diameter. The colour on the cut surface varied but was often yellowish. The consistency was usually hard and the tumour solid. However we found two cases which were cystic.

Microscopic The picture was heterogeneous. The tumour appeared encapsulated and divided into lobes by strands of connective tissue. The stroma was characterized by strands or islands of epithelial cells often simulating hair anlage. Two characteristic types of cells were seen in the islands. In the periphery were basophilic epithelial cells resembling those of the basal cell layer of the epithelium of the skin. Centrally and often numerically predominant shadow cells were seen. The cytoplasm of these cells was eosinophilic and appeared granular with well defined cell boundaries. These two cell types were present in all cases (Fig. 1).

The cell islands in about two thirds of the cases contained keratinizing foci or hornpearls (Fig. 3a). Between the cell islands sheets and bands of connective tissue and granulation tissue with foreign body giant cells were seen in



Fig. 1

Cell island with the characteristic had well (arrow) centrally surrounded by the basophilic epithelial cell

Table 1
Distribution of the material with regard to sex and age

Age	Total	Male	Female
0-5	7	3	4
6-9	3	1	2
10-19	2	1	1
20-29	1	0	1
30-39	3	0	3
40	2	2	0
	15	7	11

Duration The duration of the lesion was estimated as the time from the first examination until the excision. The average duration was 13.14 months ranging from 14 days to 10 years.

Site In most cases the information was insufficient. When described the lesion most often had a diameter of about 10 mm.

Clinical description The lesion was typically described as a solid tumour adherent to the skin but not to the underlying tissues. In one case the tumour was not movable on the underlying tissue. In one case the lesion was not adherent to the skin and in one case the tumour was described as soft.

Clinical diagnoses

Tumour unspecified	
Atheroma	4
Dermoid cyst	3
Chalazion	2
Xanthomatosis	1
Haematoma	1
	15

In the literature rare misdiagnoses are noted including neurinoma and accessory lacrimal gland.

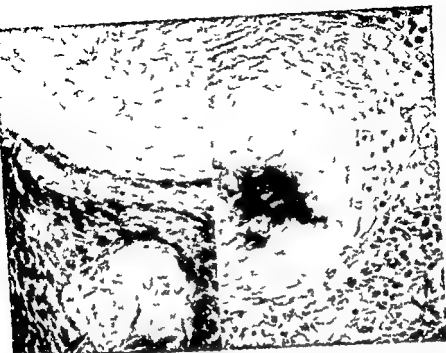


Fig 3

(a) Horn pearl situated in the epithelial cell island (b) Calcification

4) A fourth type appear as amorphous partly haemorrhagic areas and as keratin containing stands
Characteristically there are no signs of malignancy

Histogenesis

The histogenesis of calcifying epithelioma of Matherbe has been discussed for a long time Matherbe described the lesion as a calcified epithelioma originating from a sebaceous gland Turkan & Krainer (1940) suggested that the tumour originates from undifferentiated hair matrix cells Forbis & Helwig (1961) suggested the name pilomatrxoma and stated that the following features favoured the histogenesis of the tumour from hair matrix cells morphological appearance which simulates hair structure basophilic cells with a high rate of mitosis shadow cells trichohyalin droplets keratohyalin granules keratin formation birefringence under polarized light and the presence of disulphide groups

Elizabeth Holmes (1967) demonstrated the presence of citrulline in eight

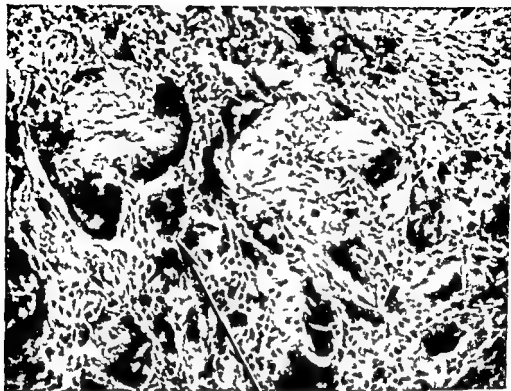


Fig 2

The heterogenous stroma with granulation tissue and foreign body giant cells (arrow)

95% of cases (Fig 2) In a few old haemorrhages were present and 95% showed calcification (Fig 3b) Melanin granules demonstrated by Masson Fontana staining were seen corresponding to the "basal cell layer" in two of the 10 stained cases Staining for citrulline was performed in three cases all showing a positive reaction

All lesions showed birefringence under polarized light in the area corresponding to the central part of the shadow cell islands The epithelial cells found in the cell islands originate from the basophilic "basal cell" In general four types of these cells have been described (Forbis & Helvig 1961 Boniuk & Zimmerman 1963) These four types were also found in the present material

- 1) Most numerous are the shadow cells described above
- 2) Some are modified to form hyalinized shadow cells These cells are transformed into a bright glassy substance in which cell boundaries cannot be identified
- 3) A third type are the squamous cells which form small groups of keratin and parakeratin often as small hornpearls These cells contain trichohyalin granules also found in the inner root sheath of hairs

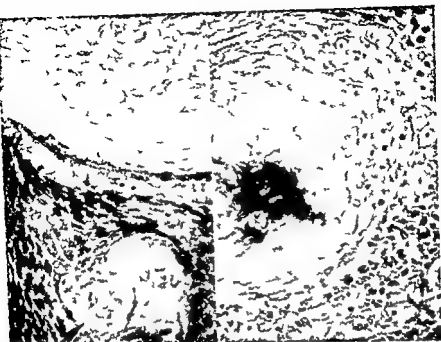


Fig 3

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4) A fourth type appear as amorphous partly haemorrhagic areas and as keratin containing stands
Characteristically there are no signs of malignancy

Histogenesis

The histogenesis of calcifying epithelioma of Malherbe has been discussed for a long time. Malherbe described the lesion as a calcified epithelioma originating from a sebaceous gland. Turkan & F rainer (1942) suggested that the tumour originates from undifferentiated hair matrix cells. Forbis & Helwig (1961) suggested the name pilomatrixoma and stated that the following features favoured the histogenesis of the tumour from hair matrix cells: morphological appearance which simulates hair structure; basophilic cells with a high rate of mitosis; shadow cells; trichohyalin droplets; keratohyalin granules; keratin formation; birefringence under polarized light and the presence of disulphide groups. Elisabeth Holmes (1967) demonstrated the presence of citrulline in eight

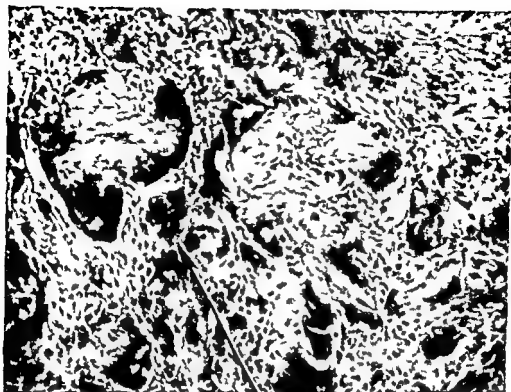


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- 1) Most numerous are the "shadow cells" described above.
- 2) Some are modified to form hyalinized shadow cells. These cells are transformed into a bright glassy substance in which cell boundaries cannot be identified.
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pilomatrixomas Keratin from the inner root sheath of hairs contains citrulline while keratin of epidermal origin does not Outer root sheath cysts and sebaceous cysts contain citrulline negative keratin The citrulline test has thus added support to the suggestion that "Epithelioma of Malherbe" originates from the hair matrix cells and the term pilomatrixoma seems well founded

Discussion

In the ophthalmological literature epithelioma of Malherbe was first described in 1957 by Ashton He found three cases from the eyelid all in females Since that time several single cases have been reported (Kornbluth & Liban 1955 Mitchell & Newell 1957 Zankan 1954 Kara 1954 Lohse & Tost 1962 Khosle & Agarwal 1963 Carbone et al 1965) Boniuk & Zimmerman (1963) described 40 cases from the eyelid and eyebrow

Firm clinical criteria for diagnosis cannot be advanced but in general pilomatrixoma should be considered when a firm tumour adherent to the skin and movable on the underlying layer is seen above the palpebral fissure in young people

Most authors state that females are predisposed sixty per cent of the present cases were females Forbis & Helwig (1961) state the age to be below 20 years in 38% and between 20 and 30 years in 43% of their cases (228 patients with pilomatrixoma on any part of the body) We found 66% under 20 years in ophthalmological patients In reports in the ophthalmological literature pilomatrixoma is usually described above the palpebral fissure We found this localization in 68% of our cases

The tumour is benign After surgical removal which is the proper treatment recurrence is seldom seen In one case from our material the lesion did recur four times

Histopathologically the tumour is interesting because of the varied histological picture and the incompletely known histogenesis From the clinical standpoint it should be a rule that all tumours from the eyelid and eyebrow are sent for histological examination Even benign looking tumours may prove to be malignant The diagnosis of pilomatrixoma is made retrospectively on histological grounds It was not made clinically in any of the present series

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PYRUVATE AND CITRATE CONCENTRATIONS IN RABBIT AQUEOUS HUMOUR DETERMINED BY AN ENZYMATIC PROCEDURE

BY

A. BRUUN LAURSEN

A modification of Moellering & Cruber's enzymatic spectrophotometric method (1966) has been employed for determining the pyruvate and citrate concentrations in rabbit aqueous humour. Aqueous humour samples from non fasting female albino rabbits of Danish country breed aged from 4 to 36 months were found to have the following concentrations (mean \pm s.d.)

pyruvate (28 animals) $339 \mu\text{mol/l} \pm 10$

citrate (28 animals) $3.4 \mu\text{mol/l} \pm 4$

glucose (9 animals) $6.1 \text{ mmol/l} \pm 0.6$ determined with a Beckmann glucose analyzer

The following concentration ratios were found in rabbit aqueous humour

pyruvate/citrate 0.98 ± 0.15 glucose/pyruvate 19.2 ± 2.2 and glucose/citrate 1.3 ± 2.5

The pyruvate/citrate ratio was found to decrease with increasing age ($0.05 > P > 0.02$)

Citrate and pyruvate determinations in the same watery pool yielded a day to day accuracy of the method expressed by coefficients of variation of 7.6% for pyruvate and 6.1% for citrate

Key words: rabbit - aqueous humour - glucose - pyruvate - citrate

Abbreviations used: NAD⁺ NADH oxidized and reduced forms of diphosphopyridine nucleotide (coenzyme I) LDH lactate dehydrogenase MDH malic dehydrogenase

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Changes of the pyruvate and citrate concentrations in aqueous humour possibly reflect alterations of the energy metabolism in the anterior eye section. In oxen the pyruvate concentrations have been found to decline and the citrate concentrations to rise with increasing age (Bruun Laursen 1972). By way of comparison the results will be reported below of determinations of pyruvate, citrate and in a few instances also glucose concentrations in rabbit aqueous humour.

Material

The pyruvate and citrate concentrations were measured in aqueous humour from 23 normal female albino rabbits of Danish country breed, aged from 4 to 36 months. In 9 of these the determinations included the glucose concentration.

To our knowledge none of the test rabbits were pregnant. Their weights ranged from 2.7 to 4.0 kg. None of the animals were fasting at the time of the chamber punctures performed between 11 o'clock a.m. and 3 o'clock p.m.

The aqueous humour samples (100–300 μ l) were obtained by puncturing the anterior chambers of local anaesthetized eyes with a fine subcutaneous cannula. The samples were immediately heated to opalescence to destroy enzymes if present. Then they were frozen down and kept in this state until the analyses were to be performed, two hours at most after the puncturing.

Methods

Pyruvate and citrate were determined by an enzymatic spectrophotometric procedure, a modification of Moellering & Gruber's (1966) method based on the following reaction stages (cf. Fig. 1).

1. $\text{Pyruvate} + \text{NADH} \xrightarrow{\text{LDH}} \text{lactate} + \text{NAD}^+$
2. $\text{Oxaloacetate} + \text{NADH} \xrightarrow{\text{MDH}} \text{malate} + \text{NAD}^+$
3. $\text{Citrate} \xrightarrow{\text{citrate lyase}} \text{oxaloacetate} + \text{acetate}$
4. $\text{Oxaloacetate} \xrightarrow{\text{oxaloacetate decarboxylase}} \text{pyruvate} + \text{CO}_2$

Oxaloacetate decarboxylase is present in the citrate lyase. The courses of reaction are shown in Fig. 1.

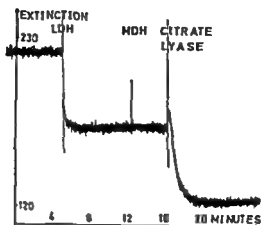


Fig. 1

Courses of the enzymic processes during pyruvate and citrate determinations on a watery solution. This assay was performed at 340 nm with quartz cuvettes (1.0 cm light path) the test cuvette containing 700 μ l triethanolamine buffer (pH \approx 7.6) 50 μ l ρ NADH solution 200 μ l H_2O and 200 μ l sample. Lactate dehydrogenase (LDH), malic dehydrogenase (MDH) and citrate lyase were added in volumes of 10 μ l.

The procedure is as stated a modification of Moellering & Gruber's method. Moellering & Gruber recommended addition of Zn^{+2} beyond the small quantities present in the citrate lyase buffer. We omitted this addition however as it was found to cause a grossly visible flocculation on addition of LDH with a resulting high extinction rise. The measurements were performed using a Zeiss spectrophotometer model PMQ II at 340 nm. Helma 103 glass cuvettes 1 cm light path. The contents of the reference cuvette were identical with those of the test cuvette except that H_2O was added instead of sample. We used enzymes and reagents from Boehringer & Sohn and from Merck. Pyruvate and citrate concentrations were calculated according to Moellering & Gruber's procedure.

To study the correlation between concentrations and extinction falls in watery solutions analyses were performed at each of six different concentration levels within the range of 50–298 μ mol citrate per litre and 63–336 μ mol pyruvate per litre. Regression analysis gave the following linear values for citrate: $y = 1.00x - 6.0$, $r = 0.996$, coefficient of variation (CV%) = 1.4. The corresponding values for pyruvate were: $y = 1.04x - 4.7$, $r = 0.997$, CV% = 0.9. The y intercepts of the citrate and pyruvate values were found not to differ significantly from zero (citrate: $0.20 > P > 0.10$ pyruvate: $P > 0.50$).

While in recovery experiments no more than three fourths of the expected extinction falls were noticed in all the simple unbuffered watery solutions about 100% of the added quantities of pyruvate and citrate were recovered in bovine aqueous humour and in serum (Tables I and II). Twenty nine duplicate determinations in bovine aqueous humour samples revealed an accuracy expressed by CV% = 1.5 within the concentration range of 10.5–269 μ mol pyruvate per litre. The corresponding value for citrate was 1.6 within the concentration range of 59–116 μ mol citrate per litre (31 duplicate determinations).

Table I
Recovery experiments in human serum

	Citrate			Pyruvate		
	$\mu\text{mol/l}$ added	$\mu\text{mol/l}$ recovered	Percentage recovered	$\mu\text{mol/l}$ added	$\mu\text{mol/l}$ recovered	Percentage recovered
	904	195	95.6	306	291	95.1
	904	211	103.5	306	296	96.7
	204	209	102.4	306	306	100.0
	204	207	101.5	306	304	99.3
	204	203	102.4	306	304	99.3
Mean	904	206	101.1	306	300	98.1
s.d.		6.4			6.4	
CV %		3.1			2.1	

To form an estimate of the day to day accuracy of the method 12 determinations were undertaken within 5 weeks on the same watery solution (stored frozen). Values were found to range from 43 to 56 μmol pyruvate per litre (s.d. = 3.9 CV % = 7.6) and from 44 to 56 μmol citrate per litre (s.d. 3.1 CV % = 6.1).

Table II
Recovery experiments in bovine aqueous humour

	Citrate			Pyruvate		
	$\mu\text{mol/l}$ added	$\mu\text{mol/l}$ recovered	Percentage recovered	$\mu\text{mol/l}$ added	$\mu\text{mol/l}$ recovered	Percentage recovered
	61	62	106.6	92	95	103.2
	61	60	98.4	92	92	103.2
	61	60	98.4	92	90	97.9
	61	55	92.1	92	89	96.7
	61	57	93.4	92	94	102.2
	61	63	103.3	92	94	102.2
	61	56	91.8	92	90	97.9
	61	60	98.4			
Mean	61	59.9	98.2	92	92.4	100.5
s.d.		3.0			2.6	
CV %		5.0			2.8	

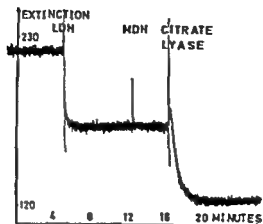


Fig 1

Courses of the enzymic processes during pyruvate and citrate determinations on a watery solution. This assay was performed at 340 nm with quartz cuvettes (1.0 cm light path) the test cuvette containing 700 μ l triethanolamine buffer (pH = 6) 50 μ l β -NADH solution 200 μ l H₂O and 200 μ l sample. Lactate dehydrogenase (LDH), malic dehydrogenase (MDH) and citrate lyase were added in volumes of 10 μ l.

The procedure is as stated a modification of Moellering & Cruber's method. Moellering & Cruber recommended addition of Zn²⁺ beyond the small quantities present in the citrate lyase buffer. We omitted this addition however as it was found to cause a grossly visible flocculation on addition of LDH with a resulting high extinction rise. The measurements were performed using a Zeiss spectrophotometer model PMQ II at 340 nm. Helma 103 glass cuvettes 1 cm light path. The contents of the reference cuvette were identical with those of the test cuvette except that H₂O was added instead of sample. We used enzymes and reagents from Boehringer & Sohn and from Merck. Pyruvate and citrate concentrations were calculated according to Moellering & Cruber's procedure.

To study the correlation between concentrations and extinction falls in watery solutions, analyses were performed at each of six different concentration levels within the range of 50–295 μ mol citrate per litre and 63–346 μ mol pyruvate per litre. Regression analysis gave the following linear values for citrate: $y = 1.00x - 6.0$, $r = 0.996$, coefficient of variation (CV%) = 1.4. The corresponding values for pyruvate were $y = 1.04x - 4.1$, $r = 0.997$, CV% = 0.9. The y-intercepts of the citrate and pyruvate values were found not to differ significantly from zero (citrate: $0.0 > P > 0.10$ pyruvate: $P > 0.50$).

While in recovery experiments no more than three fourths of the expected extinction falls were noticed in all the simple unbuffered watery solutions, about 100% of the added quantities of pyruvate and citrate were recovered in bovine aqueous humour and in serum (Tables I and II). Twenty nine duplicate determinations in bovine aqueous humour samples revealed an accuracy expressed by CV% = 1.5 within the concentration range of 105–269 μ mol pyruvate per litre. The corresponding value for citrate was 1.6 within the concentration range of 59–116 μ mol citrate per litre (31 duplicate determinations).

16	4	991	955	68	355	547	399	69	917	080	195
17	24	314	305	910	550	395	374	69	09	089	164
18	24	293	300	97	378	410	394	69	09	075	164
19	94	60	96	61	345	349	344	55	210	076	160
20	96	302	977	200	402	374	399	56	202	075	150
21	36	91	277	284	990	304	997	63	217	096	917
22	36	317	316	317	316	317	316	55	174	100	174
23	36	357	354	356	449	417	493	65	184	089	156
24	36	418	437	498	357	345	351	70	169	192	196
25	36		369	369		402	409	58	157	092	144
26	?	336	339	335	40	467	459			073	
27	?	390	359	375	407	407	407			093	
28	?	392	340	306	350	331	340			108	
Mean		339	398	339	355	458	354	61	199	098	179
± s d				± 50		± 18	± 48	± 06	± 22	± 018	± 25

Table III
Glucose pyruvate and citrate concentrations in rabbit aqueous humour

No	Age (months)	Pyruvate conc $\mu\text{mol/l}$			Citrate conc $\mu\text{mol/l}$			Glucose conc mmol/l	Ratio glucose pyruvate	Ratio pyruvate citrate	Ratio glucose citrate
		dxt	sin	mean	dxt	sin	mean				
1	4	288	288	288	359	378	368			0.78	
2	4	437	435	436	294	297	296			1.47	
3	4	281	255	268	265	256	260			1.04	
4	4	283	290	291	291	316	303				
5	4	423	408	416	300	368	339			0.96	
6	4	302	312	307	299	323	311			1.10	
7	6	399	430	415	407	371	389			0.99	
8	6	340	366	353	342	331	337			1.07	
9	6	350	305	328	331	395	388			1.05	
10	6		319	319		287	297			0.95	
11	6	333	359	346	345	354	339			1.11	
12	6	335	390	388	307	326	317			1.02	
13	6	359	354	357	328	304	316			1.22	
14	6	357	397	377	374	328	351			1.19	
15	24	331		331	414		414			1.07	
										0.80	

Pyruvate and Citrate Concentrations in Rabbit Aqueous Humour

Table IV

Data from the literature on glucose pyruvate and citrate concentrations in rabbit aqueous humour 1) methylene blue as indicator (Thunberg technique) 2) indigotin sulphate as indicator

Authors	Number of rabbits	Sample	Fasting	Glucose mmol/l ± s.d	Pyruvate μmol/l ± s.d	Citrate μmol/l ± s.d
Auricchio & De Vincenzi (1951)	4	aqueous	?		634 ± 122	
Rein et al (1972)	14	- -	?	61 ± 11	350 ± 75	
Gronvall (1937)						
1)	29	- -	—			505 ± 94
2)	36	- -	—			416 ± 51
Duke Elder (1977)	10			87		
kinsey (1953)		pooled	—			
		anterior aqueous		67		
		posterior aqueous		71		
Reddy & kinsey (1960)		pooled	?			
		anterior aqueous		54		
		posterior aqueous		57		
Bruun Laursen (1973)	23	aqueous	—	61 ± 0.6	339 ± 50	354 ± 43

In aqueous humour from oxen aged from 1 to 10 years the pyruvate concentration was found to fall and the citrate concentration to rise with increasing age. Nothing similar was detectable in aqueous humour from rabbits aged from 4 to 36 months. This may be due to the fact that no rabbits older than 3-4 years were obtainable. Considering that rabbits allegedly may live to be 8 to 10 years old the above age interval possibly represents no more than about one third of the rabbit's normal life span. As a statistically significant

Glucose determinations were performed using a Beckmann glucose analyzer (Hadish et al 1968)

Control tests on heated and then frozen rabbit aqueous humour showed the loss of pyruvate and citrate not to exceed 10% within 18 hours

Results

The results are shown in Table III

By regression analysis we searched – in vain – for correlation between the following parameters pyruvate concentration – age citrate concentration – age pyruvate concentration – weight citrate concentration – weight A significant correlation was however found between age and the pyruvate citrate ratio ($y = -0.005521x + 1.069$ $r = 0.1747$ $0.05 > P > 0.02$) the ratio becoming reduced with increasing age

The number of determined glucose concentrations is too small to allow estimating the dependence of such concentrations on age

In the series under review no difference was noticed between the mean pyruvate concentrations in the two eyes 339 $\mu\text{mol/l}$ in the aqueous humour of the right eye and 338 $\mu\text{mol/l}$ in that of the left Nor did the two eyes differ with regard to the mean citrate concentration 355 $\mu\text{mol/l}$ in the right eye and 353 $\mu\text{mol/l}$ in the left The concentration differences between the 25 paired determinations expressed by CV % were 4.6 for citrate and 4.8 for pyruvate

Discussion

The observations made by other investigators are shown in Table IV Gronvall's (1937) citrate values obtained with indigotrisulphonate as indicator Kinsey's (1953) and Reddy & Kinsey's (1960) glucose values and Reim et al's (1972) glucose and pyruvate values are in fair agreement with those found in the present material

Unlike bovine aqueous humour in which the mean pyruvate concentration is about twice as high as the mean citrate concentration rabbit aqueous humour was found to contain almost equal amounts of pyruvate (mean value 339 $\mu\text{mol/l}$) and citrate (mean value 354 $\mu\text{mol/l}$) Moreover the pyruvate and the citrate levels were both found to be considerably lower in oxen than in rabbits (Bruun Laursen 1972) This suggests a difference in metabolic pattern and level between the anterior section of the rabbit eye and that of the bovine eye

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reduction of the pyruvate/citrate ratio was noticed with increasing age the present material of rabbit aqueous humour showed the same tendency as the bovine a rising citrate concentration in proportion to the pyruvate concentration with increasing age. The individual rabbit may display distinct variations of the citrate and pyruvate concentrations at different points of time. Thus of two punctures of the same eye one revealed 320 and the other 241 μmol pyruvate per litre in the aqueous humour. In another eye citrate values of 371 and 444 $\mu\text{mol/l}$ were found (not less than 16 days between two punctures of the same eye). The pyruvate and citrate concentrations of the two eyes were generally approximately identical at a certain time although there were variations in this respect too. Such variations were seen regarding the pyruvate concentrations in rabbits 9 and 28 and the citrate concentrations in nos 14 and 17 (Table III). The stated concentration differences were beyond the mean $\pm 2.58 \times \text{s.d.}$ ($\text{s.d.} = 6.4$ i.e. the highest s.d. found in relation to determination of the accuracy of the method) for the stated differences P was less than 0.01.

These facts may have contributed towards the magnitudes of the standard deviation which also might have been less if all the rabbits had been fasting though the citrate concentrations in bovine aqueous humour were found to be in a great measure independent of the corresponding plasma levels (Bruun Laursen 1972). Variations with regard to the amounts of anterior and posterior aqueous humour in the punctures may contribute towards raising the standard deviations. However this problem cannot be solved by aspirating the same quantity of aqueous humour from all eyes because the chamber volumes are supposed to differ from one individual to another. We therefore chose to empty the chambers.

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**INCIDENCE OF DEFECTS IN THE PIGMENTED PUPILLARY
RUFF IN EYES WITH
AND WITHOUT FIBRILLOPATHIA EPITHELIOCAPSULARIS**

**(so called senile exfoliation or pseudoexfoliation of the
anterior lens capsule)**

BY

HENRY AASVED

The frequency of defects in the pigmented pupillary ruff has been studied in 15 persons with and 9462 persons without fibrillogenesis epitheliocapsularis (pseudo exfoliation). In eyes without fibrillogenesis the total frequency was 6.1% increasing from 0.7% in the age group 40-49 years to 66.4% for persons above 90. In eyes with fibrillogenesis the total frequency was far higher 74% increasing from 42% in the age group 50-59 years to 90% in patients over 90. In persons with unilateral fibrillogenesis the frequency of pupillary ruff was twice as great in eyes with fibrillogenesis as it was in those without. It is assumed that in eyes with fibrillogenesis there is an adhesion between the pigment layer of the iris and the anterior surface of the lens. Movements of the iris may then cause destruction of the iris pigment cells followed by gradual depigmentation of the pupillary ruff.

Key words: pupillary ruff defects - fibrillogenesis - exfoliation or pseudoexfoliation - normals

Defects in Pupillary Ruff

Defects in the pigmented ruff of the pupillary margin are common in elderly people. In normal subjects an increased incidence is found with increasing age from 17% in the age group 45-49 years to 56% in persons above the age of 80 (Horn 1971a).

It is usually assumed that the incidence of pupillary ruff defects is greater in patients with fibrillography (pseudo exfoliation). This has led to numerous workers considering fibrillography and the glaucoma that may accompany this condition as being the consequence of degenerative modifications in the uvea (Malling 1938, Sunde 1956, Sampaolesi 1960, Joannides et al 1961, Zlatar 1965). Others however consider that the atrophy of the iris is secondary to the effect of fibrillography (Dvorak Theobald 1954, Gillies 1962).

The literature does not however contain any large material elucidating the incidence of pupillary ruff defects in association with fibrillography. The object of this study was thus that of comparing the frequency of pupillary ruff defects in eyes with and without fibrillography.

Material and Methods

The material was collected by means of a mass screening of persons above the age of 40 and has been discussed in detail in another publication by the author (Aasved 1971). Persons with formerly diagnosed unilateral or bilateral eye disease which might influence the results of the examination were excluded.

Pupillary ruff defects were evaluated by ordinary slit lamp examination (Haag Streit 900). The light beam was adjusted at 20-30° to the axis of the microscope and was focused both straight on the pupillary ruff and to the temporal or nasal side of the pupil.

It was considered that pupillary ruff defects were present when the slit lamp examination showed distinct notches or interrupted continuity of the regular pigmented ruff allowing the typical greyish glass like membrane to be seen. Total depigmentation was registered if the pupillary ruff was missing from the whole circumference.

All subjects were examined by the author under the same examination conditions.

The material embraces a total of 8,557 persons (17,074 eyes). Among these fibrillography was found in 101 eyes in 75 persons. The frequency of pupillary ruff defects in presumably normal persons has been calculated on the basis of the 8,462 persons without fibrillography (16,974 eyes).

Results

The results showed the same tendency in both men and women. The two sexes have therefore been presented together in the tables and the analysis. The average age in the different age groups for persons with and without fibrillography appears in Table I.

Table I
Average age for persons with and without fibrillography

Age groups (years)	With fibrillography		Without fibrillography	
	Average age	s.d.	Average age	s.d.
40-49	-	-	44.6	2.8
50-59	54.9	2.5	54.9	2.9
60-69	65.0	2.6	63.7	2.8
70-79	76.0	2.4	73.6	3.0
80-89	83.7	2.7	83.7	2.8
90-99	90.0	-	92.6	3.0
Total	32		54.9	

Table II shows the frequency of pupillary ruff defects in the various 10 year age groups and the totals. In eyes without fibrillography a clear increase with increasing age can be seen from 0.7% in the group 40-49 years to 66.1% for persons above 90. Apart from a deviation in the group 60-69 years a corresponding tendency towards an increase in frequency with increasing age can also be seen in eyes with fibrillography. The frequency here is however far higher than among eyes without fibrillography and the difference has not occurred by chance ($P < 0.01$). Even in the youngest age group for eyes with fibrillography (50-59 years) the frequency is as great as in the group 80-89 years without fibrillography.

Table II
Frequency of pupillary ruff defects in mass screening material

Age groups (years)	Without fibrillography			With fibrillography		
	Examined no. eyes	With defects no. eyes	%	Examined no. eyes	With defects no. eyes	%
40-49	6152	45	0.7	-	-	-
50-59	5634	189	3.4	12	5	42
60-69	3672	307	8.5	28	21	75
70-79	906	237	26.2	30	20	66
80-89	538	214	40.0	35	31	89
90-99	47	28	66.1	2	2	100
Total	16924	1024	6.1	107	79	74

Defects in Pupillary Ruff

Table III

Incidence of pupillary ruff defects in 43 patients with unilateral fibrillography

Age (years)	Eyes without fibrillography		Eyes with fibrillography	
	No	With defects	No	With defects
50-59	8	2	8	5
60-69	8	3	8	6
70-79	16	3	16	9
80-89	11	6	11	11
Total	43	14 (32.5%)	43	28 (65%)

In view of the considerable difference in frequency the slightly higher average age of the persons with fibrillography in two of the age groups cannot have affected the comparison significantly.

The same tendency is also clearly shown in Table III which gives the incidence of pupillary ruff defects in 43 persons with unilateral fibrillography. The frequency of pupillary ruff defects is twice as great in the eyes with fibrillography (65%) as in the eyes without fibrillography (32.5%).

Among the eyes with pupillary ruff defects total depigmentation occurred more frequently in eyes with fibrillography (11 eyes = 14%) than in eyes without fibrillography (90 eyes = 8.8%).

In 68 eyes with flakes on the pupillary border defects in the pupillary ruff occurred in 56 (82%) whereas the pupillary ruffs of 12 eyes appeared to be normally pigmented.

The group of eyes with fibrillography accounted for 7.3% of the total number of eyes with pupillary ruff defect.

Comments

It has been claimed that iris pigment defects in persons below the age of 45 must be considered pathological (Norm 19:1a,b). In the present study defects in the pupillary ruff were found in 13 of 3108 eyes (0.4%) in persons aged 40-44 years none of whom were found to suffer from intraocular eye disease. The frequency in this age group is however very low and the difference between these results and Norm's finding may have occurred by chance as he investigated only 198 persons between 8 and 45 years of age.

In the eyes without fibrillography pupillary ruff defects are clearly age

determined. An increasing destruction of the pigment cells in the iris thus takes place with increasing age.

The most important finding of this study is the documentation of the very high frequency of pupillary ruff defects in eyes with fibrillography compared with eyes without fibrillography.

This finding suggests that other factors in addition to age cause depigmentation in eyes with fibrillography. It is probable that fibrillography gives the lens a more uneven anterior surface. Movements of the iris may then destroy the iris pigment cells more readily than in normal eyes. The resulting depigmentation is most clearly seen as defects in the pupillary ruff. It is also possible that fibrillar substance may penetrate the pigment layer of the iris or otherwise give a kind of adhesion between the anterior surface of the lens and the pigment layer of the iris. This mechanism may explain the massive flow of pigment into the aqueous humour sometimes seen by the author and also commented on in earlier publications (Vogt 1925, Kristensen 1965, Krause et al 1973). It also gives a satisfactory explanation of the fact that on cataract extraction in eyes with fibrillography, fractions of the pigment layer are fairly frequently found to be adhering to the anterior surface of the lens.

Pupillary ruff defects occur particularly frequently in eyes in which fibrillographic substance, the so called "flakes", can be seen on the pupillary border (82.4%). However, in such eyes the pigmented pupillary ruff may also appear completely normal as was the case in 12 of the 68 eyes with flakes in this material. The assertion that flakes are always associated with defects of the pupillary ruff (Grzedzielski 1981) is thus not correct.

The theory that fibrillography is secondary to degenerative modifications in the uvea seems improbable. In that case one would expect a relatively high frequency of fibrillography in eyes with pigment defects. In the present material fibrillography was present in only 1.3% of the total number of eyes with pupillary ruff defects. It is more probable that pupillary ruff defects in eyes with fibrillography are to some extent a result of the uneven lens surface caused by fibrillography.

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This finding suggests that other factors in addition to age cause depigmentation in eyes with fibrillography. It is probable that fibrillography gives the lens a more uneven anterior surface. Movements of the iris may then destroy the iris pigment cells more readily than in normal eyes. The resulting depigmentation is most clearly seen as defects in the pupillary ruff. It is also possible that fibrillar substance may penetrate the pigment layer of the iris or otherwise give a kind of adhesion between the anterior surface of the lens and the pigment layer of the iris. This mechanism may explain the massive flow of pigment into the aqueous humour sometimes seen by the author and also commented on in earlier publications (Vogt 1925, Kristensen 1965, Kruse et al 1973). It also gives a satisfactory explanation of the fact that on cataract extraction in eyes with fibrillography, fractions of the pigment layer are fairly frequently found to be adhering to the anterior surface of the lens.

Pupillary ruff defects occur particularly frequently in eyes in which fibrillographic substance, the so called "flakes", can be seen on the pupillary border (82.4%). However, in such eyes the pigmented pupillary ruff may also appear completely normal, as was the case in 12 of the 68 eyes with flakes in this material. The assertion that flakes are always associated with defects of the pupillary ruff (Grzedzielski 1931) is thus not correct.

The theory that fibrillography is secondary to degenerative modifications in the uvea seems improbable. In that case one would expect a relatively high frequency of fibrillography in eyes with pigment defects. In the present material fibrillography was present in only 1.3% of the total number of eyes with pupillary ruff defects. It is more probable that pupillary ruff defects in eyes with fibrillography are to some extent a result of the uneven lens surface caused by fibrillography.

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determined. An increasing destruction of the pigment cells in the iris thus takes place with increasing age.

The most important finding of this study is the documentation of the very high frequency of pupillary ruff defects in eyes with fibrillography compared with eyes without fibrillography.

This finding suggests that other factors in addition to age cause depigmentation in eyes with fibrillography. It is probable that fibrillography gives the lens a more uneven anterior surface. Movements of the iris may then destroy the iris pigment cells more readily than in normal eyes. The resulting depigmentation is most clearly seen as defects in the pupillary ruff. It is also possible that fibrillar substance may penetrate the pigment layer of the iris or otherwise give a kind of adhesion between the anterior surface of the lens and the pigment layer of the iris. This mechanism may explain the massive flow of pigment into the aqueous humour sometimes seen by the author and also commented on in earlier publications (Vogt 1925, Kristensen 1963, Krause et al 1973). It also gives a satisfactory explanation of the fact that on cataract extraction in eyes with fibrillography, fractions of the pigment layer are fairly frequently found to be adhering to the anterior surface of the lens.

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The theory that fibrillography is secondary to degenerative modifications in the uvea seems improbable. In that case one would expect a relatively high frequency of fibrillography in eyes with pigment defects. In the present material fibrillography was present in only 7.3% of the total number of eyes with pupillary ruff defects. It is more probable that pupillary ruff defects in eyes with fibrillography are to some extent a result of the uneven lens surface caused by fibrillography.

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In further studies on the sheep ERG this method has been found useful for the analysis of various effects on retinal function of neuro pharmacologically active substances and drugs e.g. alcohol (Bernhard Knave and Persson 1973) and barbiturate (Knave Nilsson and Persson 1973). Furthermore selective effects on the c wave representing the activity of the pigment epithelial cells were induced by single i.v. injections to the sheep of rifampicin a new antituberculous drug in a dose only slightly above the daily therapeutical dose used in man (Knave Persson Calissendorff and Nilsson 1973). This finding seems to confirm the melanin affinity of rifampicin proposed in an autoradiographic study by Boman (1973). The fact that rifampicin is given therapeutically for 1.5-2 years points to the necessity of studying the long term effects on the pigment epithelium and the retina of this drug experimentally and in clinical applications. This is even more important since also other drugs such as chlorpromazine and chloroquine are well known to show affinity to the pigment epithelium. In order to attack these problems clinically methods for d.c. registration of the human ERG must be developed. Clinical ERG as introduced independently by Riggs (1941) and Karpe (1945) and further developed by the latter (1948, 1967) into a routine method in general use is based upon a c registration of the a and b waves however and the electrode system employed (silver-silver chloride) does not provide the stability required for d.c. registration.

In the present paper a new method for d.c. registration of the human ERG is described. The new technique makes it possible to study the neuro retinal functions below the b wave threshold as well as the c wave and other slow potentials e.g. the so called remnant negativity (Granit and Riddell 1954) which have not earlier been investigated clinically. There are reasons to believe that this method may provide possibilities to diagnose earlier than before retinal and pigment epithelial disorders induced by drugs or caused by other factors.

Methods

Preparation of the patient

The pupils of healthy volunteers were dilated to eight mm or more with 0.5% tropicamide and 1% metaxedrine chloride given topically. A scleral contact lens (Fig. 1) modified from Knave (1970) was applied to the eye and after cleaning the skin with alcohol a plastic chamber (Fig. 1) for the tip of the reference electrode was placed on the forehead. The contact lens as well as the chamber were filled with Methocel® (Bayer AG). One of the forearms was grounded. Prior to registration the volunteer was kept in darkness for about one hour. During application of the contact lens the eye was not exposed to an illumination exceeding 5 Lux. Thereafter the eyes were allowed to dark adapt for about 40 min.

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THE HUMAN ELECTRORETINOGRAM DC RECORDINGS AT LOW AND CONVENTIONAL STIMULUS INTENSITIES

Description of a new method for clinical use

BY

BENGT KNAVE SVEN ERIK NILSSON and TÖNIS LUNT

The present paper describes in detail a new method developed for dc registration of the human EERG. In this way it was possible to investigate retinal functions that have not earlier been studied clinically, e.g. the retinal responses below the b wave threshold, the c wave and other slow potentials after cessation of the light stimulus. It is suggested that the method might lead to an earlier diagnosis than before of certain retinal and pigment epithelial disorders induced by drugs or based on other pathological conditions.

Key words: electroretinography - clinical method - retina - pigment epithelium

A re-interpretation of the major components of the EERG was recently proposed by Knave, Møller and Persson (1972). By means of subliminal light stimuli the EERG of the dark-adapted sheep eye was analysed below the conventional b wave threshold. In addition to the rod receptor potential indications of positive and negative dc responses from the inner nuclear layer were found. At stimulus intensities above the b wave threshold the c wave could be recorded as the method used was developed for dc registration of slow retinal potentials.

This investigation was supported by grants from the Swedish Medical Research Council (Projects No. 12X-734 and 04X-3119) and the Magn Bergvall Foundation.
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In further studies on the sheep ERG this method has been found useful for the analysis of various effects on retinal function of neuro pharmacologically active substances and drugs e.g. alcohol (Bernhard Knave and Persson 1973) and barbiturate (Knave Nilsson and Persson 1973) Furthermore selective effects on the c wave representing the activity of the pigment epithelial cells were induced by single i.v. injections to the sheep of rifampicin a new antituberculous drug in a dose only slightly above the daily therapeutical dose used in man (Knave Persson Calissendorff and Nilsson 1973) This finding seems to confirm the melanin affinity of rifampicin proposed in an autoradiographic study by Boman (1973) The fact that rifampicin is given therapeutically for 1.5-2 years points to the necessity of studying the long term effects on the pigment epithelium and the retina of this drug experimentally and in clinical applications This is even more important since also other drugs such as chlorpromazine and chloroquine are well known to show affinity to the pigment epithelium In order to attack these problems clinically methods for d.c. registration of the human ERG must be developed Clinical ERG as introduced independently by Riggs (1941) and Harpe (1945) and further developed by the latter (1948 1969) into a routine method in general use is based upon a c registration of the a and b waves however and the electrode system employed (silver-silver chloride) does not provide the stability required for d.c. registration

In the present paper a new method for d.c. registration of the human ERG is described The new technique makes it possible to study the neuro retinal functions below the b wave threshold as well as the c wave and other slow potentials e.g. the so called remnant negativity (Granit and Riddell 1934) which have not earlier been investigated clinically There are reasons to believe that this method may provide possibilities to diagnose earlier than before retinal and pigment epithelial disorders induced by drugs or caused by other factors

Methods

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Key words: electroretinography - clinical method - retina - pigment epithelium

A re-interpretation of the major components of the FRC was recently proposed by Knave, Møller and Persson (1972). By means of subliminal light stimuli the ERG of the dark adapted sheep eye was utilised below the conventional b wave threshold. In addition to the rod receptor potential indications of positive and negative d.c. responses from the inner nuclear layer were found. At stimulus intensities above the b wave threshold the c wave could be recorded. As the method used was developed for d.c. registration of slow retinal potentials

This investigation was supported by grants from the Swedish Medical Research Council (Projects No. 12X-634 and 04X-9119) and the Magn Bergvall Foundation.
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Fig 3

To the left the tip of the recording electrode with a surgical swab filling made so as not to touch the cornea. To the right the tip of the reference electrode with the surgical swab filling protruding to make a wide contact area with the forehead.

Recording system

Matched calomel half cells were used as recording and reference electrodes. They were connected to the contact lens and the plastic chamber on the forehead by means of saline bridges in agar filled polyethylene tubes about 60 cm in length (Fig 2 and 4). These bridges changed for every volunteer, assured that calomel could not reach the eye.

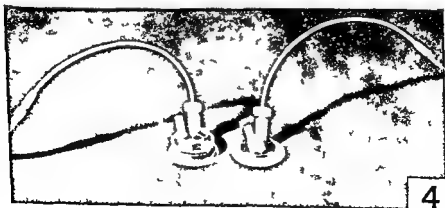


Fig 4

The electrode tips in their holders.

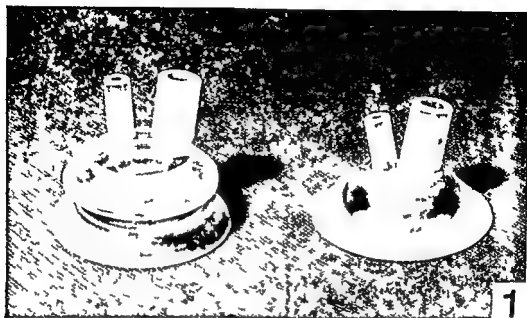


Fig 1

The scleral contact lens to the left and the plastic chamber for the forehead to the right. Each has a holder for the electrode tip (the recording and the reference electrode resp) and a small tube which may serve as a fluid reservoir.

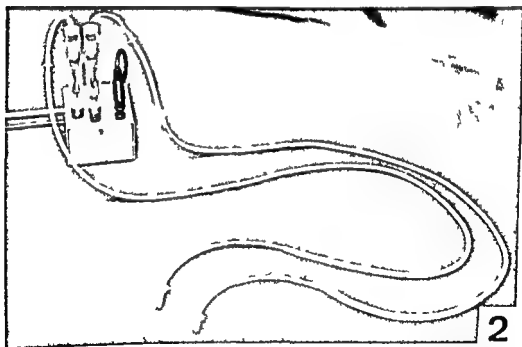


Fig 2

The matched calomel half cells used as recording and reference electrodes. Between the electrode tip and the half cell is a saline bridge in an agar filled polyethylene tube.

DC Recording of the Human ERG

Pieces of surgical swab (Sponcal) were put in the tips of the recording tubes to ensure a good contact with the Methocel® (Fig 3 and 5) The swab was not allowed to touch the cornea

The polyethylene tube holder on the contact lens was always placed temporally so as not to obscure the pupillary area (Fig 6) A shielding wire net cage was lowered over the head and upper part of the volunteer and over the electrode system in order to exclude artefacts from alternating current etc (Fig 11)

The electrodes were connected to the differential inputs of a low drift d.c. amplifier. The potentials were lowpass filtered (990 Hz cut off 18dB/octave) and fed into a Hewlett Packard signal analyzer 5490S. The display screen of this signal analyzer was photographed with a polaroid camera (Fig 4) For possible future need of a more

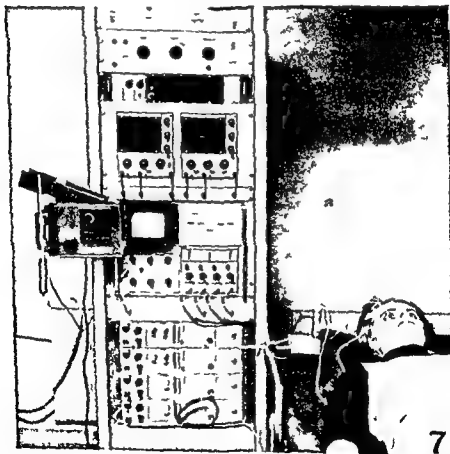


Fig 2

The all metal half cells are connected to the pre-amplifier. The rack contains (from the bottom) four low drift d.c. amplifiers, a Hewlett Packard signal analyzer, two additional electronic modules and electronics for the trigger system and for the stimulus light shutter.

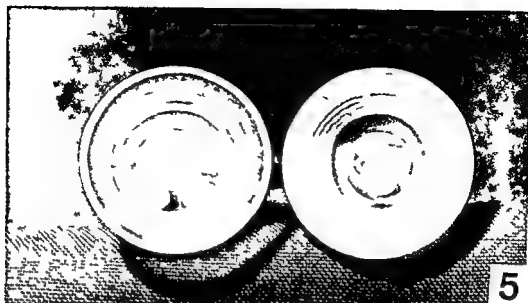


Fig 5

The contact lens and the chamber for application on the forehead seen from the inside
The electrode tips in place



Fig 6

The contact lens on the eye The chamber into which is led the tip of the reference electrode is attached to the forehead by means of a ring shaped two sided adhesive tape

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The polyethylene tube holder on the contact lens was always placed temporally so as not to obscure the pupillary area (Fig 6) A shielding wire net cage was lowered over the head and upper part of the volunteer and over the electrode system in order to exclude artefacts from alternating current etc (Fig 11)

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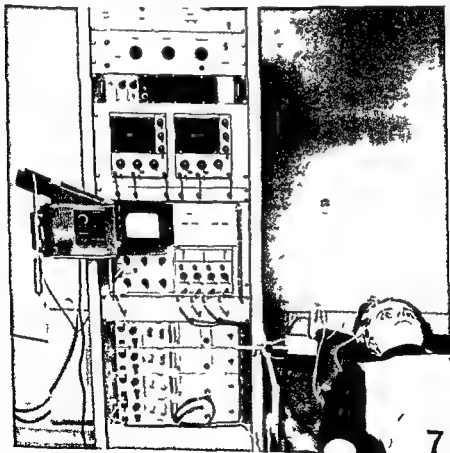


Fig 7

The alomel half cells are connected to the pre amplifier The rack contains (from the bottom) four low drift d.c. amplifiers a Hewlett Packard signal analyzer two additional oscilloscopes and electronics for the trigger system and for the stimulus light shutter

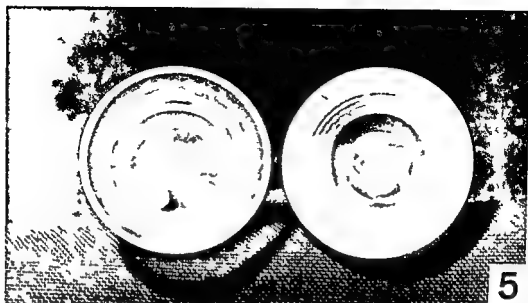


Fig 5

The contact lens and the chamber for application on the forehead seen from the inside
The electrode tips in place



Fig 6

The contact lens on the eye The chamber into which is led the tip of the reference electrode is attached to the forehead by means of a ring shaped two sided adhesive tape

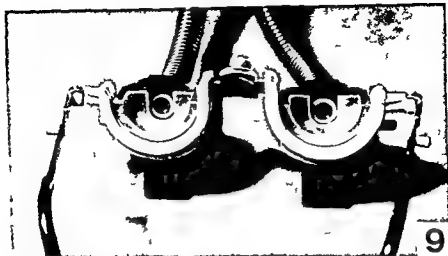


Fig 9

The fiber optics attached to an adjustable spectacle frame (ordinarily used for refractions) The tips of the fiber optics can be adjusted to fit the position of the pupils

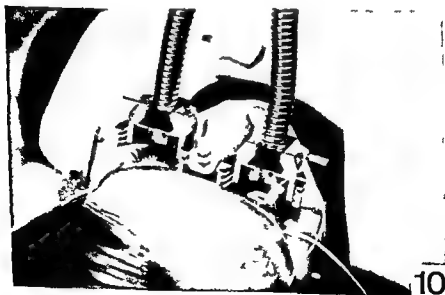


Fig 10

A volunteer prepared for dc recording of the electroretinogram

detailed computer analysis the output was also punched on a paper tape. The noise level of the electrode system was 5–10 μV and the d.c. drift 10–15 $\mu\text{V/hr}$. Four to 50 responses were usually averaged in the signal analyzer before taking a photograph.

Stimulus light

A 150 Watt ozone free Osram HBO xenon lamp with an approximately flat spectral emission curve within the visible part of the spectrum was used for light stimulation. A heat reflection filter and a heat absorbing filter (Zeiss) were placed in the light beam. The light intensity was changed by means of neutral density filters (Balzer). The intensity eliciting a single flash b wave (threshold at 30–40 μV) is referred to as log relative intensity 0. A Zeiss electromagnetic shutter (placed in a focal plane of the beam) was used to control the stimulus duration which in the records of the present study was kept at one sec (except in Fig. 12A where the duration was 0.1 sec). The rise time as well as the fall time of the light stimulus was less than 10 msec. The interval between the test flashes was 10 sec for log relative intensity -0.5 , 30 sec for log relative intensity 0.5 and 2 min for log relative intensity 4.5.

The stimulus light was led to the eyes of the volunteer through a Y shaped quartz fiber optics (Schott) with a total length of 100 cm and with a fiber bundle diameter of 10 mm at the common end and 5 mm at the two separate ends (Fig. 8). This arrangement

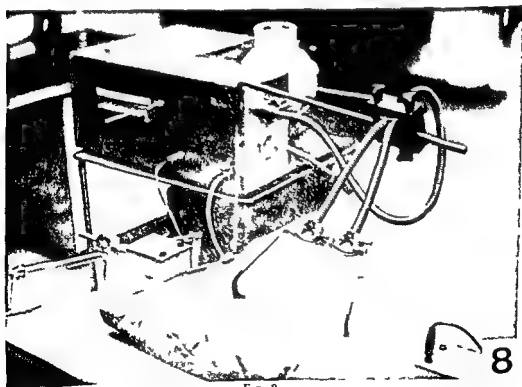


Fig. 8

The stimulus light unit including a xenon lamp, filters, an electronic shutter, and a fiber optics attached to a spectacle frame.

A 2.2 msec stimulus current was used as a short event duration and a 1-wire electrode was used at the nearest corneal cells. Noel and others also used a 2.2 msec stimulus.

The ERG in response to a stimulus with an intensity of -1.0 relative log units is demonstrated in Fig. 13A. A positive d.c. shift at all of the same duration as the light stimulus is seen superimposed on a slow, cornea-negative, and with an amplitude maximum at -1.0 sec after cessation of light. The ERG response below the conventional 2-wire threshold well corresponds to the slow wave ERG of the same name by Evans, Miller and Pearson.

There are reasons to believe that the cornea-negative potential corresponds to the receptor potential and that the positive d.c. shift during light stimulation corresponds to the so-called positive d.c. response of the slow ERG.

Fig. 13B shows a recording just above the b-wave threshold (-1.0 relative log units) at this intensity level the configuration of the ERG response is similar to the slow wave ERG demonstrated in Fig. 13A. However, the positive d.c. shift now exceeds the conventional threshold (-1.0 μV) in electroretinography and is in all part thus represents the b-wave of the ERG. The slow wave shift following the positive d.c. potential corresponds to the remnant response first described by Granit and Riddell (1954).

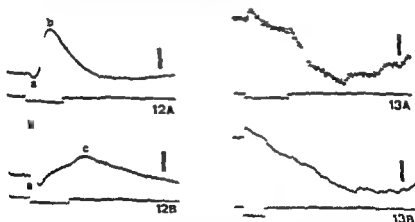


Fig. 13

The recorded human ERG in response to a relative stimulus intensity of about -1.0 log units at the b-wave threshold. Stimulus duration (indicated on lower line) 0.1 sec (A) and 1.0 sec (B). Amplitude calibration $50 \mu V$.

Fig. 13

The recorded human ERG in response to a relative stimulus intensity of about -1.0 log units below (A) and above (B) b-wave threshold. Stimulus duration 1.0 sec. Amplitude calibration $5 \mu V$ (A) and $50 \mu V$ (B).

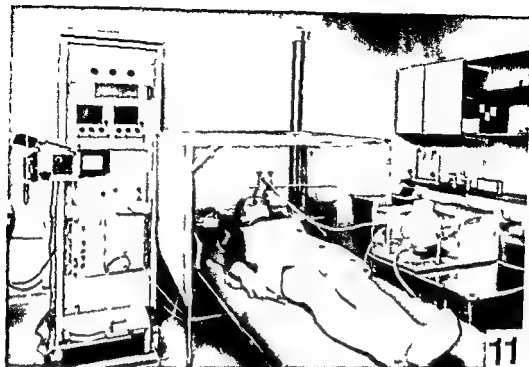


Fig 11

A shielding wire net cage is lowered over the volunteer and the electrode system to exclude artefacts from alternating current etc

made it possible without loss of light of the shorter wave lengths to control more accurately the light reaching the pupil. The tips of the fiber bundles facing the eyes were fixed at a distance of 20 mm from the cornea by means of an adjustable spectacle frame (Figs 8-10). The fiber tips could be adjusted in two planes so as to fit precisely the position of the pupils. For the purpose of obtaining a wide angled uniform light stimulus the contact lens was made slightly opaque. Experiments have shown that the shape and the amplitude of the ERG responses did not change if a thin opaque light scattering filter was applied to the surface of the contact lens. Fig 11 shows the entire set up in a survey picture.

Results and Discussion

The results will be presented and discussed mainly in following papers. In the present paper some typical responses will be shown only to demonstrate the main features and possibilities of the new method of recording the human ERG.

The d.c. recorded human ERG in response to a relative stimulus intensity of 4.5 log units is shown in Fig 12. With a stimulus duration of 0.1 sec and a sweep time of 0.45 sec a small a wave and a predominant b wave are seen.

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EIN EINFACHES HILFSMITTEL BEI DER BEURTEILUNG VON KRÜMMUNGSANOMALIEN DER HORNHAUT

VON

W J PAWELSKI

Mittels Spaltlampenaufnahmen bei Krümmungsanomalien der Hornhaut wurde das Erscheinungsbild der Linsenvorderfläche demonstriert. Es konnten drei charakteristische Formen dieses optischen Phänomens gezeigt werden: eine Abflachung, eine Konkavität und eine wellenformige Veränderung.

Key word: Anomalien der Corneacurvature – optisches Phänomen – diagnostisches Hilfsmittel

Auch erfahrenen Untersuchern können die ersten Entwicklungsstadien des Keratokonus oder Keratoglobus diagnostische Schwierigkeiten bereiten. Hierbei wie auch bei anderen Anomalien der Kurvature der Cornea hat es sich bei uns bewährt, während der Spaltlampenuntersuchung mit dem optischen Schnitt das Erscheinungsbild der Linsenvorderfläche zu beobachten.

Abweichungen von der normalen Kurvature der Cornea führen zu einer charakteristischen Veränderung des Spaltbildes der Linsenvorderfläche, die bei einem Winkel von 10° und mehr zwischen Beleuchtungsstrahlengang und Beobachtungsstrahlengang bei weiter Pupille gut sichtbar ist.

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Abb a-c

Scheinbare Konkavität der Linsenvorderfläche a) Hornhautschnittfoto Aufnahmewinkel b) 30° c) 10° Patient 40 Jahre ♀ Befund akuter Keratokonus rechts Ophthalmometerwert rechtes Auge nicht messbar Visus rechtes Auge Handbewegung 1/2 m Hinhaut. Zentrale Verdünnung des Stromas mittelblasiges Epithelödem in einem runden etwa 1 mm Ø grossen zentralen Gebiet Stromaquellung durch alle Schichten Sternfigur nach 1. und 1.° h feine Descemetfaltung im gleichen Gebiet

Amsler (1938) betonte dass das charakteristische Zeichen für den Konus auch für den leichtesten Grad immer die in Winkelgraden messbare Knickung der waagerechten Achse des Placido Bildes sei

Interessant in diesem Zusammenhang ist eine Mitteilung von Mandell und Hise (1979) in der die Meinung vertreten wird dass die frühe Form des Keratokonus nicht durch eine zentrale Hornhautdickenmessung erkannt werden kann. In den meisten Fällen wurde dies auch nicht durch das Handkeratoskop



Abb 1a-c

Scheinbare Ablenkung der Linsenvorderfläche Aufnahme Winkel a) 20° b) 40° und c) 60° Patient 19 Jahre ♂ Befund Keratokonus links Ophthalmometerwert linkes Auge 44 5 1,5° 55 5/50° Visus linkes Auge sc 0 1(1 Z) Glasz und Sieb bessern nicht Hornhaut Oberfläche glatt zarte Verdünnung der Cornea im Zentrum hier auch feine Descemetfalten

Da die Kenntnis dieser scheinbaren Veränderung der Linsenvorderfläche – im folgenden kurz als optisches Phänomen bezeichnet – die Untersuchung wesentlich erleichtert sie aber in der Literatur unseres Wissens nach bislang nicht näher beschrieben wurde mochten wir kurz darauf hinweisen

Es kann ohne Frage keines der bekannten Verfahren zur Diagnostik und Messung der Hornhautanomalien ersetzen insbesondere nicht die Auswertung photokeratoskopischer Bilder nach der Amsler'schen Graduierung des Keratokonus



Abb. 1 a-c

Scheinbare Konkavität der Linsenvorderfläche a) Hornhautschnittfoto Aufnahme win-
kel b) 40° c) 60° Patient 40 Jahre Q Befund akuter Keratokonus rechts Ophthal-
mometerwert rechtes Auge nicht messbar Visus rechtes Auge Handbewegung 1/2 m
Hornhaut Zentrale Verdünnung des Stromas mittelblaues Epithelödem in einem
runden etwa 2 mm Ø grossen zentralen Gebiet Stromaquellung durch alle Schichten
Sternfigur nach 6 9 und 12 h keine Descemetfaltung im gleichen Gebiet

Veisler (1935) betonte, dass das charakteristische Zeichen für den Konus
auch für den leichtesten Grad immer die in Winkelgraden messbare Knickung
der waagerechten Achse des Placido Bildes sei.

Interessant in diesem Zusammenhang ist eine Mitteilung von Mandell und
Tolse (1947), in der die Meinung vertreten wird, dass die frühe Form des Ke-
rat Konus nicht durch eine zentrale Hornhautdickenmessung erkannt werden
kann. In den meisten Fällen wurde dies auch nicht durch das Handkeratoskop



Abb 3a-c

Scheinbare Welligkeit der Linsenvorderfläche (gleichsinnige Veränderung der Rückfläche) 1) Hornhautschnittfoto Aufnahme Winkel b) 10° c) 30° Patient 21 Jahre 3 Befund Keratokonus links Ophthalmometerwert linkes Auge nicht messbar Visus linkes Auge sc 0,2 mit Sieb 0,4 (2 Z) Hornhaut Peripherie klar zentral sehr dünn verzweigte zentrale Trübungen Descemet geknittert

das Photokeratoskop und die Keratometrie gelingen jedoch sei die Messung der Hornhautdicke über den gesamten horizontalen Meridian wertvoll

Abweichungen der Hornhautdicke um 0,05 mm zwischen Zentrum und einem 35° entfernten Ort können für den Keratokonus als pathognomonisch gelten

Die folgenden Spaltlampenphotographien zeigen das beobachtete optische Phänomen in drei Erscheinungsformen in einer scheinbaren Abflachung (Abb 1a-c) Konkavität (Abb 2a-c) oder wellenförmigen Veränderung der Linsen

vorderfläche (Abb. 3a-c) Noch deutlicher tritt es allerdings in Erscheinung wenn unter verschiedenen Einfallswinkeln beobachtet oder photographiert wird oder wenn man das Spaltbild über die Hornhaut bewegt

Die Aufnahmen wurden mit der Photospaltleuchte vom VEB Carl Zeiss Jena bei einem Abbildungsmaßstab von 10 aufgenommen Als Filmmaterial verwendeten wir für die Cornea Spaltaufnahmen den NP 15 und für die Spaltaufnahmen des gesamten vorderen Augenabschnittes den NP 27 (VEB ORWO Wolfen) Die Spaltbreite betrug bei allen Aufnahmen 0,1 mm Die untersuchten Augen wurden vertikal Mitte Cornea optisch geschnitten und der Mikroskopteil (gleichzeitig Aufnahmeteil) der Photospaltleuchte wurde in vorgewählten Winkeln jeweils nach temporal hin ausgeschwenkt

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Abb 3a-c

Scheinbare Welligkeit der Linsenvorderfläche (gleichsinnige Veränderung der Rückfläche) a) Hornhautschnittfoto Aufnahmewinkel b) 10° c) 30° Patient 21 Jahre ♂ Befund Keratokonus links Ophthalmometerwert linkes Auge nicht messbar Visus linkes Auge sc 0,2 mit Sieb 0,1 (2 Z) Hornhaut Peripherie klar zentral sehr dünn verzweigte zentrale Trübungen Descemet geknittert

das Photokeratoskop und die Keratometrie gelingen jedoch sei die Messung der Hornhautdicke über den gesamten horizontalen Meridian wertvoll

Abweichungen der Hornhautdicke um 0,085 mm zwischen Zentrum und einem 35° entfernten Ort können für den Keratokonus als pathognomonisch gelten

Die folgenden Spaltlampenphotographien zeigen das beobachtete optische Phänomen in drei Erscheinungsformen in einer scheinbaren Abflachung (Abb 1a-c) Konkavität (Abb 2a-c) oder wellenförmigen Veränderung der Linsen

The aim of the medical prescription for a unilateral contact lens is to give the patient the ability to use both of his eyes. However, before recommending or prescribing a contact lens, it is important to estimate whether, in fact, the aid will be of any real use to the patient. This is as true for unilateral lenses as it is for bilateral contact lenses.

When discussing the problem of treating unilateral aphakia, the binocular problem should be outlined. Here a contact lens is conceived as a therapy for aniseikonia, and isekonia must be of minor importance unless bifoveal vision is present. This concept is maintained by Keith Lyle, who in 1953 made an orthoptic study of patients treated for aphakia with contact lenses and contended that an estimation of the binocular vision is of great prognostic importance for the success of the treatment.

An orthoptic examination made in advance may reveal whether suppression, scotoma or diplopia are present. Furthermore, a major amblyoscope may be valuable in general contact lens practice to indicate whether an artificial hyperphoria is present due to decentering of a heavy low riding plus lens.

Suppression scotoma creates a complete stereo acuity loss, and with it the refined distance judgment. It must be recognized that monocular vision is preferred if diplopia is present.

Further attention must be paid to how much the surplus of the temporal extension of the ipsilateral visual field given by a lens can counterbalance a fading initial enthusiasm, as well as the inconvenience and minor risk which is associated with contact lens wearing.

In cases of anisometropia, for other reasons – of unilateral keratoconus and irregular or scarred cornea – the binocular problems are essentially the same.

The incidence of squint in the general population is about 1%. It is a well known fact, however, that the fusional range, even in adults, may disorganize when an eye has been deprived of useful vision as a result of sustained imperfection of the refracting media. Thus we can predict a greater prevalence of deficient binocular vision among patients who are primarily referred for unilateral contact lens fitting.

The hypothesis put forth here is that unless there is good binocular function, the rate of success in unilateral contact lens treatment will not be high. The exception to this hypothesis is the advent of aphakia in younger children suffering from a penetrating corneal injury. Without treatment, these children are doomed to a life long state of amblyopia in one of their eyes. Provided we are able to establish an alternating strabismus with a contact lens, the risk that amblyopia will recur is minimal.

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THE BINOCULAR FUNCTION AS AN INDICATOR FOR THE SUCCESS OF AND NEED FOR UNILATERAL CONTACT LENSES

BY

V DREYER

Ninety five patients were referred for fitting with unilateral contact lenses. One half of the patients had non traumatic aphakia, a quarter of them had traumatic aphakia and the rest had anisometropia or reduced vision for other reasons. Wearing a trial lens all patients were examined at the major amblyoscope prior to prescription.

In prescribing a unilateral contact lens the aim is to re-establish a useful binocular vision. Pre-existence of certain qualities of binocularity is thus considered to be a prerequisite for success. In consequence of this about 30% of the patients were rejected primarily mainly because of strabismus. This rather high frequency exceeds the general incidence of squint and points to the fact that the fusional range even in adults may disorganize when one eye has been deprived of useful vision. To prove this hypothesis a contact lens was tried in a number of patients even though their binocular state was doubtful. Follow up studies demonstrated that simultaneous perception near zero degree, a fusional range around 20 pd and stereopsis were found to have an ever increasing rate through the groups of unsuccessful to successful cases. Thus an orthoptic study must not be underestimated as an indicator for the success of unilateral contact lens prescription.

Key words: contact lenses unilateral - binocular vision - unilateral aphakia

Table II

The diagnosis of cases fitted with unilateral contact lens

Non traumatic aphakia	52
Traumatic aphakia	25
Anisometropia of other reasons	8
Corneal scars	5
Keratoconus	2
Keratoplasty	1
Neuroparalytic keratitis	2
	95

tion of the centering of the lens and its excursions and in addition epithelial damage and more modifications in 10%.

In all cases of unilateral contact lens prescription an evaluation of the binocular state was established by means of the cover test and with the major amblyoscope. The orthoptist examined the patients when they were wearing a trial lens and the three classical qualities of binocular vision were studied. The subjective and objective angle of simultaneous perception if any was recorded as well as the angle of fusion and the fusional range with small fusional objects. Finally the presence or absence of stereopsis was tabulated.

In the evaluation of the results of the orthoptic survey imperfections of the trial lens due to displacement were examined. The fusional range was considered to be of the greatest importance. This examination is rather independent of imperfections of the trial lens. The binocular state was often reevaluated when the patient wore his final lens.

The Danish Tribunal of Disablement Insurance defrays the expenses for the purchase of contact lenses when the aid may remedy a disablement to a considerable degree. From a medical point of view this provision has been interpreted to mean that in cases requiring a unilateral lens some degree of binocular vision must be present with the exception only of cases in which prevention of amblyopia is concerned.

As a result of this policy very few patients need to be without useful therapeutic lenses. However some patients are not considered suitable for contact lenses - specifically those with suppression scotoma, anomalous retinal correspondence or simultaneous perception in some visible negatively or positively deviating angle as measured from the zero point.

Material and Results

The material presented here comes from patients fitted with unilateral contact lenses at the University Eye Clinic Rigshospitalet Tagensvej Copenhagen

Table I shows the distribution of age and sex among the 95 patients. More men than women are represented particularly in the ages of 40 to 60.

Table II gives the diagnosis of the examined patients. The largest number was found in the group of non-traumatic senile cataract. Most of these patients were operated upon using cryo-surgical technique and a visual acuity of 6/6 followed surgery in almost all cases.

The second largest diagnostic group was that of traumatic cataract. These patients, often young, were referred from the surgical department as soon as possible after surgery, usually after a month. After linear cataract extraction combined with aspiration of lens masses, the pupil was frequently black following one or more surgical sessions. In some cases fibrous capsular remains were divided with Vannas technique.

All the patients were examined by the author. Those fitted with contact lenses were fitted by the author according to the method of Samson, Soper & Girard based on topographic reading. In our experience this method is the quickest and the best suited for clinical purposes. With this method there was need for only one prescription with no modification in about 60% of the cases (Dreyer 1970). In 30% one modification was needed on the basis of an estimate.

Table I

The distribution of age and sex among patients examined

Age	Number	Women	Men
< 10	2	1	1
11-20	12	3	9
21-30	14	5	9
31-40	11	2	9
41-50	10	10	9
51-60	10	5	11
61-70	10	5	5
> 70	5	3	5
	95	40	55

Table IV

The result of the orthoptic analysis in relation to the success of contact lens wearing

	Primarily rejected	Unsuccessful	Successful
Simultaneous perception			
None or in deviating angle	91%	74%	*46%
0 ± 3 pd	9%	26%	54%
Total fusional range			
< 3 pd	60%	23%	16%
6 - 10	35%	21%	24%
> 20 pd	5%	56%	60%
Stereopsis			
Correct	15%	35%	70%
Incorrect	85%	65%	30%
No simultaneous perception only one patient			

to the successful patients. Conversely a simultaneous perception near zero degree has an increasing rate through the groups from successful to rejected. A fusion range around 20 pd is seldom found among the rejected patients and is common among the successful group. Correct stereopsis is infrequent in the rejected group but more frequent in the unsuccessful group. Inharmonious and malous retinal correspondence was not found perhaps because most of the patients were adults. However no single orthoptic quality can be predictive of success. Simultaneous perception for instance should be considered in comparison with the fusional range because a high fusional range can offer compensation for a considerable deviation of the angle. On the other hand small fusional reserves are sufficient when simultaneous perception takes place around zero degrees. Furthermore a certain build up of the fusional range is possible when the patient starts to wear the contact lens all day.

Stereopsis is not always possible to obtain by first examination. As mentioned the trial lens can provoke hyperphoria and prevent stereopsis of small objects. Even the final lens may adjust to the cornea better as time goes by.

Thus the results obtained by an orthoptic study must be regarded as an estimate and its practical value as an indicator for the success of contact lens fitting must not be underestimated.

Young persons exposed to perforating injuries often demonstrate simultaneous perception in a sizable angle deviating from the zero point but with a normal fusional range around it. Such patients often are treated by strabismus surgery prior to the contact lens fitting and so can benefit totally.

Table III demonstrates the result of a simple cover and uncover test. The patients have been divided into three subgroups: 1. patients initially rejected because of a breakdown of binocular vision; 2. patients in whom a contact lens was tried even though the state of their binocularity had been doubtful and in whom the prescription was found later to be unsuccessful; 3. successful patients that is those who wear the lens all day without trouble or corneal damage.

This table shows an ever increasing percent of orthophoria or minor heterophoria as we go from the rejected to the successful patients. Considerable degrees of heterophoria are seen in the unsuccessful group as this group was recruited from patients with uncertain binocular function.

Squint concerns the majority of the cases found among the rejected patients with success found only in the treatment of strabismus in children being treated for amblyopia.

Eye muscle paralysis was considered to be a contraindication for contact lens wearing in anisometropia because the better the visual acuity of the affected eye the more pronounced the diplopia. Thus the simple cover test seems to be a good indicator for the possible success of a unilateral contact lens.

Table IV indicates the different results obtained by examining the three steps of orthoptic analysis in the three subgroups arranged according to the increasing ability to wear contact lenses. Where simultaneous perception is concerned we find a high percentage of suppression or a considerable deviation from the zero point of the subjective-objective angle of simultaneous perception in the rejected group with the numbers diminishing from the unsuccessful group.

Table III
The result of the cover and uncover test

	Primarily rejected	Unsuccessful	Successful
Total number	25	29	38
No or minor heterophoria	33%	54%	79%
Considerable heterophoria	6%	29%	16%
Strabismus	56%	17%	5%
Paralysis	8%	0%	0%

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Discussion

If in clinical practice we find a patient who had sustained an eye injury 30 years previously and now desires a cataract extraction mostly for cosmetic reasons the prognosis for wearing contact lenses may be considered very poor as orthoptic analysis usually will confirm that he has no binocularity left

It may well be argued that every contact lens fitter knows people who are very satisfied and wear their lenses all day even though theoretical considerations may indicate that the lens is useless

This genuine problem is well known in medical practice The choice between a treatment that makes a patient happy and a treatment which is scientifically supported depends upon the side effects of the treatment and its economic consequences Every physician knows that a happy patient is often a patient who feels that somebody takes care of him

In this connection it may also be argued that the material here presented is based on the fact that some patients were excluded without trying to demonstrate whether a prescription would be a success or not Thus the excluded patients can be discussed using the same philosophy and the same question can be raised about what actually is a successful fitting

This exclusion however is justified if the preselection is made purposely to exclude patients who cannot obtain bifoveal vision nor make use of the possible isekonia we can offer them

Furthermore if simultaneous perception can be demonstrated in a high deviation angle and no fusional range can compensate this fact the patient would suffer diplopia if a lens was prescribed

It is well known that considerable degrees of heterophoria give rise to intermittent double vision when the fusion breaks down Patients are seldom aware of this symptom however and complain instead that they have eye strain fatigue conjunctival sensations and so forth Except for cases of low riding lenses even contact lens patients seldom list double vision among their complaints

Nonetheless two major theoretical points should be emphasized 1 good binocular vision is a decisive factor for the successful fitting of unilateral contact lens 2 a preliminary orthoptic study will often reveal deficiencies in the binocular state and therefore a lack of this knowledge may make it difficult to help a patient who maintains that "there is something wrong with this lens"

OPHTHALMOLOGICAL ASPECTS ON ERGOMEDICAL PROBLEMS

B. L. Nave Long term Changes in the Electroretinogram Induced by High Intensity Light

The results of the present report show that short high intensity electronic flashes are followed by reversible long term changes in the retinal function. A method was evolved by which the ERG of the intact rabbit eye could be recorded over a period of several months. It was shown that a single light flash with an intensity of 7 log units above the threshold of the b wave of the dark adapted eye was followed by a slight reduction of the b wave which lasted for about a week. An additional 10 flashes (2/min) of the same intensity resulted in a slight initial increase of the b wave. The initial increase was more pronounced following 100 flashes with intensities of 8 and 9 log units above the b wave threshold. In the latter experiment the initial increase lasted about 49 h (with a maximum 3 h) after the exposure. Following this increase a transient decrease was noted and recovery to pre illumination values was accomplished in 9 weeks.

Similar long term changes were noted in the b wave threshold i.e. a decreased excitability which was preceded by an increased excitability after the exposure to 100 flashes. Moreover the flash effects described above were seen in pigmented as well as albino rabbits and no difference was noted after optic denervation. Thus the effects described are not due to influences of a shielding pigment or an efferent mechanism.

It was proposed that the reversible long lasting changes in retinal function described in the present report might be due to a light induced damage of the photoreceptor cell outer segments.

S. F. Nilsson The Risk of Retinal Damage Following Exposure to Light

It has been demonstrated earlier (Noell 1966 Kuwabara et al 1969) that animals mainly albino rats show retinal damage following exposure to light even cool light of only moderate brightness (150-1000 foot candles). After one days exposure pronounced ultrastructural changes were seen in the receptor outer segment. When the exposure was 3 to 5 days the entire outer segment became degenerated and the inner segment showed marked pathological changes. A good recovery of the structures occurred only when the exposure to cool light was less than 12 hours. Nave (1970) found long term biphasic effects of a small number of high intensity flashes on the ERG of the rabbit (albino and pigmented ones). An initial increase of the b wave amplitude was followed by a decrease lasting 1 to 9 weeks. An ultrastructural investigation was undertaken to determine whether these ERG changes were correlated to morphological changes.

Young pigmented mice were exposed to 950 high intensity electronic photo flashes. The flashes were given during 1 hour at a distance of about 90 cm from the dilated pupil of the eye. Three to 9 days later the eyes were fixed by means of perfusion with glutaraldehyde and prepared for electron microscopy. Neither the retina nor the pigment epithelium showed any ultrastructural signs of damage whatsoever.

The receptor outer segments are known to be continuously renewed by synthesis of new membranes at the base and by incorporation of old disc into the pigment epithelium at the tip of the outer segment (Nilsson 1964 Young 1964). The turn over time is about 30 days for mice. The process of renewal was somewhat faster when the animal had been exposed to light at a brightness of 600 foot candles for 8 days than when the animals had been kept in total darkness (Young 1964).

TRANSACTIONS OF
THE SWEDISH OPHTHALMOLOGICAL SOCIETY
1972

BY

BJÖRN SVEDBERGH Secretary

Meeting in Norrköping March 18 - 19 1972

PHOTOCOAGULATION AND DIABETIC RETINOPATHIA

B Zetterstrom *50 Cases of Diabetic Retinopathy Treated with Photocoagulation*

Photocoagulation was carried out on 50 patients with bilateral symmetrical diabetic retinopathy. Their ages ranged from 21 to 70 years. Only one eye was treated in each case, comparing the response with the condition of the untreated fellow eye. The degree of severity of retinopathy varied. Changes such as microaneurysm, retinal oedema, yellow exudate, dilated blood vessels, retinal neovascularisation not involving the vitreous and intra retinal and preretinal hemorrhages were present. Cases which showed formation of new vessels or connective tissue proliferation into the vitreous were excluded.

The follow up period was 1 to 9 years. All patients were followed up with fundus photographs in colour, estimation of visual acuity and fluorescein angiography. These procedures showed a clear cut remission of retinopathy in 64% of the cases, no improvement in 26% and progression of the lesions in 10%. As regards the situation in the untreated fellow eye the corresponding percentages were 14%, 41% and 15% respectively.

■ Stenkula and K Tornquist *The Prognosis of Photocoagulation Treatment of Proliferative Diabetic Retinopathy*

E Östberg *The Effect of Photocoagulation on the Vitreous Body in Diabetic Retinopathy*

In the summer of 1970 15 workers from the radar transmitter in Karlskrona were examined in the ophthalmic department of the Central Hospital in Karlskrona Sweden. The 15 workers were examined before their summer vacation and during or immediately after it. This was to verify reversible and/or irreversible pathological changes before the vacation. 10 out of 15 workers showed round or oval negative absolute scotomas bilaterally in the visual fields and two patients showed unilateral scotomas. After the vacation only one patient showed bilateral scotomas and another one had a unilateral scotoma.

In two patients the slit lamp revealed a few very fine whitish irregular filaments immediately behind the lens showing arborization with nodes and thickening in a vertical direction. Very fine punctate retinal or choroidal scars whitish yellow in colour were seen in the central parts of the fundus in two patients and a third patient showed a small cystic degeneration in the macular region simulating a macular hole without affecting his visual acuity. None of the workers complained of eye symptoms and all of them were apparently in excellent physical condition. But 8/15 showed high ESR (erythrocyte sedimentation rate) 5/15 gave positive AST (antistreptolysin titre) and 8/15 gave positive ASTa (antistaphylolysin titre).

I Rendahl *A Case of Microwave Induced Cataract?*

A. Dyster Aas *Ergophthalmology - Is There a Need?*

VARIA

T Jerndal E Lindstedt T Svensson and G Åkerskog *Presentation of the Retinoblastoma Material in Sweden*

B Rosengren *An Attempt with Light Absorbing Spectacles at Pigment Degeneration*

Meeting at Malmö June 3-4 1972

INTRAOCULAR HYPERTENSION - GLAUCOMA

E Linnér *The Intraocular Pressure*

B Bengtsson *The Importance of High Intraocular Pressure in a Normal Population*

T Jerndal *Criteria for Glaucoma Simplex*

Glaucoma simplex has by definition an open angle and lacks any obstructive tissue in the angle. Any other ocular disease must be excluded. Gonioscopy is therefore necessary and should be meticulously performed in order to disclose discrete anomalies e.g. exfoliations, hypoplasia of the iris stroma, coloboma or persistent angle membrane (Barkan's membrane) which puts the case in the category of congenital glaucoma. Thus open angle glaucoma is not equivalent to glaucoma simplex. Approximately 90% of glaucomas with an open angle are exfoliation glaucoma, 40% late congenital glaucoma and a mere 40% true glaucoma simplex.

In the present study the turnover rate of the outer segments of eyes of mice exposed to 250 electron flashes was compared with that of unexposed control eyes. The turnover rate was determined by following in electron microscope autoradiography the displacement along the outer segment of a radioactive reaction band representing incorporated labeled amino acids. There was no difference between exposed eyes and control eyes with respect to outer segment turnover rate.

In summary it can be concluded that high intensity flashes which are known to cause long term effects on the ERG of rabbits did not give rise to any ultrastructural changes in the mouse retina or to any changes in outer segment turnover rate.

(This investigation was supported by a grant from the Swedish Medical Research Council Project No B12-12\-,34-06)

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B Tengroth Welding and Protective Spectacles

E Aurell *The Effect of Microwave Radiation on the Eye*

A general description was made of the physical and biological properties of the microwave radiation. The effect on the eye was especially discussed. Some of the experimental studies of the cataractogenic effect of the microwaves were reviewed, as were the investigations made by Clark and Zaret of the prevalence of lens defects in people occupationally exposed to microwave radiation. It was stated that no other effects on the eye have been described.

The author examined 54 workers exposed to microwaves during work. Five of them were found to have central or paracentral changes in the eyes. Two men were aware of paracentral scotomas; one had reduced visual acuity, V.A. = 0. The average age for these five men was below 30 years. Whether these retinal changes are due to microwave radiation is so far only a hypothesis. Further investigations must be carried out with control series and such investigations have been started.

Finally the author emphasized the biological hazards with this radiation and concluded that further restrictions are to be expected for the uncontrolled use of microwave radiation.

S Alani *Vitreo Retinal Injuries Due to Microwave Radiation*

The damage to personnel exposed to microwave radiation is nowadays of great concern. During the last 25 years extensive experimental studies of animals have shown that poorly vascularized tissues such as the crystalline lens may easily be damaged by microwave radiation. Lesions such as posterior subcapsular opacities of the lens and even complete cataracts have been reported. Even damage in the anterior parts of the eye such as the cornea, iris and anterior chamber have been noted. However to my knowledge no pathological changes or damage posterior to the lens have been reported at least not in human beings.

known as the melatonin produced in the epiphysis and acting as an inhibitor to the hypothalamic pituitary hormone system

The production and release of melatonin is directed by light impulses from the retina transmitted via sympathetic innervation to the epiphysis. When light is on viz. in the daytime the melatonin synthesis is off. This means that the inhibition of the hypothalamus ceases and the hormonal hypothalamic activity goes on viz. stimulation. This is the neuro endocrine background for our circadian rhythm maybe also in the eye. Further investigation has to prove this.

B Becker and O Holm *Some Relations Between Excitation of the Papilla and Visual Field Defects*

A. Wettrell *Glaucoma Patients with Visual Field Defects. A Retrospective Study*

One hundred patients with glaucomatous visual field defects have been studied retrospectively. Special attention has been paid to initial symptoms and findings and to the condition of the fellow eye in cases of monocular glaucoma.

C E T Krakau *On Automatic Testing of the Visual Field*

The problem of automatic screening of the visual field has been approached. It seems probable that a high percentage of the cases with early glaucomatous defects might be found by determination of the threshold at only very few points (say 4-6) in the field.

A first version of a field screener has been constructed. It is based on a two alternative system (one or two lightspots left or right sided stimulus). The patient has to press one of two buttons corresponding to the alternative he chooses. The fixation is controlled by placing one test light in the blind spot which should not be seen at correct fixation.

L Frisén *Kinetic Perimetry Reproducibility* (Based on the article *Forced Motion Attachment for the Goldmann Perimeter* - *Ophthalmologica* (Basel) 63 (1972) 487-491)

J Christiansson *Fistulizing Operations in Advanced Cases of Glaucoma*

It is very hard to put forward some general rules for the attitude towards these patients. However, both patient and doctor will benefit from a more careful evaluation of the remaining vision and central field. Both qualities are important for the function of the eye. The author has found static quantitative perimetry very useful, offering a better evaluation of the operative risk. Fistulizing surgery has been performed without endangering the point of fixation in cases where the remaining visual field is bordering upon the centre and the visual acuity is at least 0.5.

L Halldén *Iridotomy with a New Knife at Irresistible Operation*

VARIATION

S Stenkula and R Tornquist *Trials of Tissue Glue in Eye Surgery*

A Hedin *Illumination at Colour Vision Test* (L. Frisén & A. Hedin *Illumination Tests for colour vision tests* - *Acta ophthalmologica* (Kbh) 50 (1972) 570-574)

L. Berggren *Critical Flicker Frequency (CFF) in Man During Ocular Hypertension*

The individual susceptibility to raised intraocular pressure was studied using a new technique CFF was registered centrally and in the Bjerrum area using a photostimulator and flash lamp device. An acute rise in intraocular pressure was induced by dynamometry. During the experiment the intraocular pressure was controlled by applanation tonometry. Normal test subjects were examined under standard conditions and at different IOP levels. The individual CFF values were registered and the test subject served as his own control. In normal subjects an abrupt decrease in CFF was noted above 40 mmHg. There was no evidence that the CFF level during dynamometry was affected by changes in pupil size, astigmatism or refractive error. It is suggested that the cause of the decrease in CFI during acute ocular hypertension might be due to vascular changes in the eye.

K. Wilke and C. E. T. Krakau *Intraocular Pressure Changes During Repeated Tonometry* Acta ophthalm (Kbh) 50 (1972) 514-519

H. Bynke, C. E. T. Krakau and K. Wilke *Repeated Applanation Tonometry in Optic Atrophy* Acta ophthalm (Kbh) 50 (1972) 240-246

S. Osterlin *Studies on the Angle of the Interior Chamber of the Eye - Biochemical Composition and Metabolism of the Connective Tissue Structures*

To gain access to Schlemm's canal the aqueous must pass the juxtacanalicular tissue. The macromolecules of this connective tissue layer will offer resistance to aqueous flow and it was therefore considered important to study the nature of these macromolecules and their metabolism. Biochemical analysis of an analogue structure from bovine eyes has shown that this tissue contains glucosaminoglycans as well as galactosaminoglycans. It is now a well established fact that the glycosaminoglycans appear in the tissues covalently bound to a protein core. The biodegradation and removal from the tissues of these macromolecules, the proteoglycans, takes place by degradation of the protein core. The role of extracellular proteases of lysosomal origin in this process has been amply verified. With the use of a micromethod such proteoglycanases were demonstrated in aqueous from owl, monkeys, rabbits and cattle. There is a possibility that local application of steroids and other agents known to influence the permeability of the lysosome membrane might change the concentration of proteoglycanases in the aqueous and the juxtacanalicular tissue.

E. Godtfredsen *Ophthalmopinealogy: Carcic and Circadian Aspects Including the Intraocular Pressure*

The normal pathophysiology of the intraocular pressure is a standing challenge to all ophthalmologists. Much is known about how and when the intraocular pressure varies, the phasic cyclic diurnal or circadian changes (the last term comes from the latin *circa diem* around the day). Why these changes happen we in fact know very little about. Here modern pinealogy may be of assistance to ophthalmology.

Research during the last ten years has established the pineal body or epiphysis as a biological clock, a neuroendocrine transducer responsible for many of our circadian rhythmic variables, the plasma cortisol, the serum iron etc. This motivates a short outline of the natural history of the pineal body from the day of René Descartes to modern neurobiochemistry, which has found a new hormone, a serotonin derivative.

known as the melatonin, produced in the epiphysis and acting as an inhibitor to the hypothalamic pituitary hormone system

The production and release of melatonin is directed by light impulses from the retina transmitted via sympathetic innervation to the epiphysis. When light is on viz. in the daytime, the melatonin synthesis is off. This means that the inhibition of the hypothalamus ceases and the hormonal hypothalamic activity goes on viz. stimulation. This is the neuro endocrine background for our circadian rhythm maybe also in the eye. Further investigation has to prove this.

B Becker and B Holm *Some Relations Between Excavation of the Papilla and Visual Field Defects*

L. Wettrell *Glaucoma Patients with Visual Field Defects. A Retrospective Study*

One hundred patients with glaucomatous visual field defects have been studied retrospectively. Special attention has been paid to initial symptoms and findings and to the condition of the fellow eye in cases of monocular glaucoma.

C. E. T. Krakau *On Automatic Testing of the Visual Field*

The problem of automatic screening of the visual field has been approached. It seems probable that a high percentage of the cases with early glaucomatous defects might be found by determination of the threshold at only very few points (say 4-5) in the field.

A first version of a field screener has been constructed. It is based on a two alternative system (one or two lightspots left or right sided stimulus). The patient has to press one of two buttons corresponding to the alternative he chooses. The fixation is controlled by placing one test light in the blind spot which should not be seen at correct fixation.

L. Frisén *Kinetic Perimetry. Reproducibility* (Based on the article "Forced Not on Attachment for the Goldmann Perimeter" *Ophthalmologica* (Basel) 65 (1972) 43-45).

J. Christiansson *Fistulizing Operations in Advanced Cases of Glaucoma*

It is very hard to put forward some general rules for the attitude towards these patients. However, both patient and doctor will benefit from a more careful evaluation of the remaining vision and central field. Both qualities are important for the function of the eye. The author has found static quantitative perimetry very useful, offering a better evaluation of the operative risk. Fistulizing surgery has been performed without venturing the point of fixation in cases where the remaining visual field is bordering upon the centre and the visual acuity is at least 0.5.

U. Hallidén *Iridotomy with Narrow Knife at Indolent Operation*

VARIA

S. Stenkula and R. Tornquist *Trials of Tissue Glue in Eye Surgery*

A. Hedin *Illumination at Colour Vision Test* (L. Frisén & A. Hedin, Illumination box for colour vision tests. *Acta ophthalmol.* (Abh.) 50 (1972) 570-574).

L Berggren *Critical Flicker Frequency (CFF) in Man During Ocular Hypertension*

The individual susceptibility to raised intraocular pressure was studied using a new technique CFF was registered centrally and in the Bjerrum area using a photostimulator and flash lamp device An acute rise in intraocular pressure was induced by dynamometry During the experiment the intraocular pressure was controlled by applanation tonometry Normal test subjects were examined under standard conditions and at different IOP levels The individual CFF values were registered and the test subject served as his own control In normal subjects an abrupt decrease in CFF was noted above 40 mmHg There was no evidence that the CFF level during dynamometry was affected by changes in pupil size astigmatism or refractive error It is suggested that the cause of the decrease in CFF during acute ocular hypertension might be due to vascular changes in the eye

K Wilke and C E T Krakau *Intraocular Pressure Changes During Repeated Tonometry* Acta ophthal (Kbh) 50 (1972) 574-582

H Bynke C E T Krakau and K Wilke *Repeated Applanation Tonometry in Optic Atrophy* Acta ophthal (Kbh) 50 (1972) 240-246

S Österlin *Studies on the Angle of the Anterior Chamber of the Eye - Biochemical Composition and Metabolism of the Connective Tissue Structures*

To gain access to Schlemm's canal the aqueous must pass the juxtacanalicular tissue The macromolecules of this connective tissue layer will offer resistance to aqueous flow and it was therefore considered important to study the nature of these macromolecules and their metabolism Biochemical analysis of an analogue structure from bovine eyes has shown that this tissue contains glucosaminoglycans as well as galactosaminoglycans It is now a well established fact that the glycosaminoglycans appear in the tissues covalently bound to a protein core The biodegradation and removal from the tissues of these macromolecules the proteoglycans takes place by degradation of the protein core The role of extracellular proteases of lysosomal origin in this process has been amply verified With the use of a micromethod such proteoglycanases were demonstrated in aqueous from owl monkeys rabbits and cattle There is a possibility that local application of steroids and other agents known to influence the permeability of the lysosome membrane might change the concentration of proteoglycanases in the aqueous and the juxtacanalicular tissue

E Godtfredsen *Ophthalmopinealogy Carotic and Circadian Aspects Including the Intraocular Pressure*

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Research during the last ten years has established the pineal body or epiphysis as a biological clock a neuro endocrine transducer responsible for many of our circadian rhythmic variables the plasma cortisol the serum iron etc This motivates a short outline of the natural history of the pineal body from the day of René Descartes to modern neurobiochemistry which has found a new hormone a serotonin derivative

and neurons in the retina (Kaneko & Hashimoto 1969 Kaneko 1970 and review Tomita 1970) are however unclear. In order to analyze the ERG components further we have applied a new method in which the details of the ERG could be studied at intensities well below the b wave threshold.

In a recent work (Knave 1970) a technique for corneal recording of the ERG was developed which was shown to give constant amplitude values in iterative long term experiments. In the present study a combination of this method and the averaging technique was applied to record low intensity ERGs in sheep within an intensity range 2.5 log units below the b wave threshold of the dark adapted eye. The conventional ERG of the light adapted eye was also studied before and after raising the intraocular pressure.

The results indicated five basic components of the ERG = the rod and cone receptor potentials, a positive and a negative d.c. (direct current) response from the inner nuclear layer and a late slow positive response corresponding to the conventional c wave at higher stimulus intensities. It is suggested that the leading edge of the a wave constitutes the initial phase of the cone receptor potential. The b wave is assumed to result from the integration of the receptor and d.c. responses and it is assumed to be built up mainly by the positive d.c. response.

The components proposed in the present study have functional characteristics similar to the retinal potentials led off intracellularly from the receptor and inner nuclear layers.

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M Gjöterberg and P Alqvist: *Oscillatory Potentials and Fluorescein Angiography. A Clinical Study of Diabetic Retinopathy*

The amplitude of the oscillatory potentials of the electroretinogram is known to be affected by disturbances of the retinal circulation. The oscillatory potentials have been reported to be subnormal or even extinguished in diabetics with or without an ophthalmoscopically visible retinopathy.

The aim of the present work was to study the oscillatory potentials at different stages of proliferative diabetic retinopathy. One eye of 25 patients was studied. Most patients had juvenile diabetes and the duration of the disease was in all cases at least 5 years after puberty. The type of retinopathy was classified according to the findings obtained by ophthalmoscopy and fluorescein angiography. Twenty two patients had a normal visual acuity (0.7 or more).

In retinopathy with signs of incipient neovascularization demonstrating leakage of fluorescein from micro aneurysms in the retina the amplitude of the oscillatory potentials was slightly reduced. In eyes showing distinct proliferative retinopathy with formation of new vessels within the retina visible at ophthalmoscopy the oscillatory potentials were reduced more than in the previous group of incipient proliferative

Meeting in Stockholm December 2 1972

I Rendahl *What is locomotor vision?*

II Wulfig *Experiences with Hydrophil Contact Lenses*

III Philipsson *Lens Changes in Senile Cataract*

P Alqvist *Retinal Detachment Following Experimental Occlusion of Retinal and Choroidal Vessels in Monkeys*

The clinical detachment of the retina is usually associated with a retinal break. The incidence of retinal tears or holes is however much higher than that of retinal detachment. An isolated retinal break is not necessarily followed by a detachment unless other pathological changes e.g. in the vitreous retina or choroid accompany the lesion.

Experiments were carried out in owl monkeys (*Aotus trivirgatus*). The hyaluronic acid of the vitreous was degraded by hyaluronidase. By means of a micro surgical procedure spheric polystyrene beads ($1-25 \mu$ in diameter) were injected into the central retinal artery at the site where the artery enters the optic nerve in the orbit. Part of the choroidal circulation was blocked by injecting such plastic beads into the superior temporal vortex vein.

The embolization of retinal vessels caused ischemia, oedema and focal hemorrhages in the inner retinal layers. The occlusion of the circulation in one sector of the choroid was followed by subretinal exudation and degeneration in the outer layers of the retina. After degradation of the hyaluronic acid and occlusion of retinal vessels vitreous detachment and formation of vitreous strands were observed and circumscribed detachments of the retina developed at the posterior pole of the fundus. In another series of experiments the hyaluronic acid of the vitreous was degraded by the enzyme and 7-12 days later a combined occlusion of retinal and choroidal vessels was performed. This procedure was followed by a total funnel shaped detachment of the retina within a week. The eyes showed severe vitreous pathology such as heavy strands and invasion of inflammatory cells as well as accumulation of subretinal fluid rich in cells and protein.

In addition to the retinal break the following pathogenetic factors seem to be of importance for the development of a retinal detachment: (i) The attractive forces between the neuro retina and the pigment epithelium. These forces were affected by the choroidal ischemia leading to pathological changes of the pigment epithelium and receptor cells. (ii) Firm vitreo retinal adhesions. Such adhesions were observed after focal ischemia in inner retinal layers and vitreo retinal juncture. (iii) Retinal traction from vitreous structures. Vitreous strands developed after focal retinal ischemia and after hyaluronidase treatment these strands became thicker and showed a conspicuous invasion by inflammatory cells.

(This work was supported by the Swedish Medical Research Council - project No B 72-60R-3655 -)

B Knave, A Möller and H Persson *A Component Analysis of the Electroretinogram*

The gross ERG has been shown to be composed of several component potentials of different signs and amplitudes (Granit 1933, Brown 1968). The relations between these components and the recently studied intracellular responses from the receptors

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NEW COMPRESSION TESTS IN GLAUCOMA

II Posterior annular compression test

BY

A P NESTEROV G A KISELEV AND E R DEVLIKAMOVA

The posterior annular compression test aims at estimating the aqueous outflow facility as well as at detecting the predisposition to the closure of the anterior chamber angle. An annular compressor weighing 50 g is placed on the globe in a posterior position to the iris lens diaphragm for 3 min. In 115 normal eyes the intra ocular pressure dropped after the test by 2 % or even more and the volume of the eyeball decreased not less than 5.5 mm³ designating the limits for a negative test. In patients with open angle glaucoma the test was positive in 86% of the 58 eyes examined. However in all these cases a decrease of the intra ocular pressure occurred. The tension and the volume of the globe increased or remained unchanged in 35 eyes of the total of 52 with chronic closed angle glaucoma.

Key words: glaucoma diagnosis - compression of the eye - annular compression tests

Several annular compression tests have been described (Rosengren 1934 1956 Sobanski Swietliszko & Szosland 1957 Zarubin 1965). In each of them the outside pressure is applied to the perilimbic area. As the latter is a portion of the front wall of the anterior chamber the above techniques can be called the anterior annular compression tests. During the tests the anterior chamber

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retinopathy The only eyes in which the oscillatory potentials were extinguished were those that exhibited preretinal proliferative vascular and fibrous changes

The degree of leakage of fluorescein from retinal tissue (vessels) was estimated and compared with the amplitude of the oscillatory potentials There seemed to be a good correlation between increasing leakage of dye and the reduction of the amplitude of oscillatory potentials

J Snobohm *Transconjunctival Retinal Cryopexy at Slit Lamp Biomicroscopy*

N Rawal L Heijman and E Wold *Clinical Experience with Ketamine Anaesthesia in Ophthalmology*

A potent analgetic and anaesthetic agent ketamine® has been used for ophthalmic surgery as an alternative to the usual intubation anaesthesia Sixty nine patients most of them children under 14 years of age were operated on under ketamine anaesthesia The patients were divided into three groups to study the influence of different pre medications on anaesthesia and the postoperative recovery An induction dose of 2 mg/kg i.v. or 10 mg/kg i.m. ketamine was given As a routine the maintenance dose was 1 mg/kg i.v. but the dose varied with the type and duration of the operation In some cases especially for intraocular surgery local anaesthetic agents were also employed The study was carried out in association with a paediatric psychiatrist and a psychologist who studied the psychic effects of ketamine in about one third of the patients

Ketamine has proved to be a good analgesic and anaesthetic agent There is slight or no depression of the protective reflexes the airway is maintained easily respiration is unaffected and there is cardiovascular stability except for some increase in blood pressure No significant complications were observed pre or postoperatively In a number of cases we noted an increased mobility of the eyeball which could be prevented by using a Superior Rectus suture or by giving local anaesthesia The latter also minimizes the slightly increased operative bleeding which may occur In a few cases we noticed temporary psychic side effects postoperatively and the day after the operation

Ketamine appears to be a good complement to other anaesthetic agents due to its simple administration its low toxicity and its few side effects particularly for eye surgery in children Since the children are not intubated the problems associated with intubation are not encountered and the children wake up quietly without coughing and with a low incidence of vomiting all of which are important factors in ophthalmic surgery

O Holm *One Years Experience of Optacon a Reading Aid for Totally Blind*

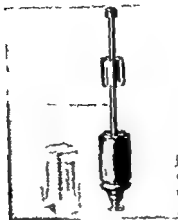


Fig 1

The annular compressor Left the cup of the compressor right the load and the holder (the Vurgast sclero compressor)



Fig 2

The position of the annular compressor on the eye

angle is supposed to become wider as in the case when the outside pressure is applied to the cornea (Torres 1966; Lakomkin 1969). The anterior annular compression tests causing the blockage of the anterior outflow channels are mainly employed for measuring the aqueous inflow and the suction cup technique by Rosengren (1956) and Ericson (1958) appears especially valuable.

The purpose of the technique now to be described is to displace the iris lens diaphragm forward and to estimate the aqueous outflow facility under such conditions. It may be assumed that the new technique makes it possible to reveal the predisposition to the angle closure. This technique is called the posterior annular compression test because the outside pressure is applied behind the iris lens diaphragm and is transmitted to the posterior wall of the anterior chamber.

Material and Methods

An annular compressor has been designed (Fig. 1). It consists of a cup, a load and a holder. The inner diameter of the cup is 16 mm and the outer diameter is 17 mm. The contact surface of the cup is slightly beveled. It has two breaks 5 mm long to diminish the influence of the compression on the circulation in the conjunctival and episcleral blood vessels. The Vurgift sclero compressor (Vurgift 1952) serves as a load and a holder. The weight of the compressor equals 50 g.

The procedure is briefly as follows. The patient was placed on the table in a recumbent position. Two or three measurements were obtained with the MacLakov tonometer. The annular compressor was then placed on the eyeball so that the corner was in the centre of the cup (Fig. 2). After 3 min the compressor was removed and the measurements with the tonometer were taken again. The changes of the intraocular pressure and the volume of the eye (ΔV) were calculated making use of the new calibration table for the MacLakov tonometer (Nesterov & Vurgift 1972; Nesterov, Churbanov & Kolotkov 1972).

The test was carried out in 115 normal eyes of 100 persons from 24 to 70 years of age (mean 46 years) in 32 eyes of 28 patients with early primary closed angle glaucoma, in 20 eyes of 17 patients with advanced closed angle glaucoma and in 58 eyes of 46 patients with primary open angle glaucoma, 38 eyes being in the early stage of the disease and 25 eyes in the advanced stage. Glaucoma was considered to be in its early stage if there was no glaucomatous cupping of the optical disk and no noticeable field loss.

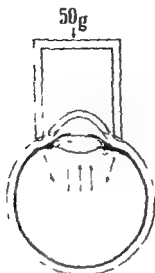


Fig 3

Schematic view of the posterior annular compression test

Recently the prone provocative test has been described. This test involves nonmydriatic mechanisms and was positive in 50-70% of the eyes with closed angle glaucoma (Hyams, Friedman & Neumann 1968; Harris & Galin 1972). However, the prone provocative test is a time-consuming procedure. It takes more than an hour to perform. We have had personal experience with this test. Some of our patients could not endure the prone position for a whole hour. We made an attempt to shorten the duration of the procedure to 15 min instead of 1 hour. However, no positive results were observed in 22 patients with primary closed angle glaucoma. The posterior annular compression test seems to be a more convenient technique for detecting the predisposition to angle closure in routine practice.

Due to the large size of the inner diameter of the annular compressor, the outflow channels are not subject to compression and the load is applied behind the iris-lens diaphragm. The pressure in the posterior part of the globe increases and the iris-lens diaphragm moves forward (Fig 3). In predisposed eyes, the angle may be blocked by the iris root. Due to a considerable rise in tension during the test, the rate of aqueous production decreases. This effect diminishes the efficiency of the posterior annular compression technique.

The new technique proved to be a valuable test for early detection of primary closed angle glaucoma. It can also be used for the diagnosis of chronic

Results

The results are summarized in Table I. In healthy eyes the ΔV values were 9.93 ± 2.21 mm³ (the mean \pm s.d.). The following diagnostic criteria have been found. In normal eyes (1) the ΔV value must not be less than 5.5 mm³ and (2) the decrease of the intra ocular pressure is 22% or even more.

The test was positive in 27 eyes (92%) with early open angle glaucoma and in all but two (92%) with advanced open angle glaucoma. The ΔV values ranged from 1 mm³ to 10.8 mm³ with the mean value of 2.21 mm³.

The data obtained in eyes with closed angle glaucoma were of major interest. In the early stage of the disease the positive result of the test was observed in all but two cases. The intra ocular pressure and the volume of the eyeball increased in 12 eyes, remained unchanged in 11 eyes and decreased only in nine eyes. In eight eyes of total 20 with advanced angle closure glaucoma the intra ocular pressure and the volume of the globe decreased. In the other 12 cases both indices either increased or remained unchanged.

Discussion

Several techniques for early detection of closed angle glaucoma are described. Most of them involve pupillary dilatation either by darkness or by the use of mydriatics (Higget 1951, Corin 1965, Kirsch 1965). However, the efficiency of each of these tests is low (Ustinova 1966). Besides, any mydriatic agent can provoke an uncontrollable attack of angle closure.

Table I

Results of the posterior annular compression test in normal and glaucomatous eyes

Diagnosis	No. of eyes	Volume changes (mm ³)	
		Mean	s.d.
Normal eyes	115	- 9.93	2.21
Open angle glaucoma			
(1) early	33	- 2.10	1.97
(2) advanced	25	- 2.02	1.86
Closed angle glaucoma			
(1) early	32	+ 2.01	1.65
(2) advanced	20	+ 1.91	1.12

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OPHTHALMOLOGICAL FINDINGS IN INFANTILE TYPE
OF SO CALLED
NEURONAL CEROID LIPOFUSCINOSIS

BY

CHRISTINA RAITTA and PIIRKKO SANTAVUORI

The ophthalmological findings in 16 children with infantile type of neuronal ceroid lipofuscinosis are presented. All patients showed signs of a progressive encephalopathy with onset at the age of 8-18 months. Visual failure, ataxia, muscular hypotonia, microcephalia and myoclonic jerks were typical findings. Fluorescein angiography showed narrowing of the retinal vessels and pigmentary dystrophy as well as optic atrophy. The site of the primary defect was thought to be the pigment epithelium and receptor cells. The ERG was abolished.

Key words: amaurotic idiocy - infantile neuronal ceroid lipofuscinosis - receptor cell layer - pigment epithelium - ERG in neuronal ceroid lipofuscinosis - fluorescein angiography in neuronal ceroid lipofuscinosis

A number of cases of early onset have been described by Santavuori et al 1973 apparently constituting a clearly separable group within the so called neuronal ceroid lipofuscinosis (NCL) (Zeman & Dyken 1969). These cases differ from

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open angle glaucoma but in this case its efficiency seems to be about the same as in other bulbar pressure tests

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the established types of NCI i.e. the Bielschowsky Jansky Spielmeier Sjogren and Kufs types by their clinical onset at about one year of age early amaurosis and relative paucity or absence of convulsions. Morphologically they are characterized by early neuronal destruction massive occurrence of phagocytes and heavy astrocytosis in the cerebral cortex. The neurons and phagocytes contain excessive amounts of a granular storage substance with the tinctorial properties of lipofuscin but with a homogenous granular ultrastructure (Haltia et al 1973).

This paper deals with the ophthalmologic findings in patients with infantile NCI including the results of fluorescein angiography and electroretinography.

Material and Methods

The present series consists of 16 children aged from 18 months to 4 years seven were girls and nine were boys. In all cases the diagnosis was based on characteristic histological histochemical and ultrastructural findings in brain biopsies. All the patients showed signs of a progressive encephalopathy with onset at the age of 8-18 months characterized by rapid psychomotor deterioration ataxia muscular hypotonia visual failure as well as microcephalia and myoclonic jerks. Some children had convulsions for a short period but most of the children had no fits. The characteristic electroencephalographic features were the slowing and diminution of the rhythmic activity rapidly approaching isoelectricity as well as absence of any reaction to photic stimulation in a very early phase of the disease.

Ophthalmological examination included evaluation of vision eye motility biomicroscopy when possible and ophthalmoscopy. In our youngest patients the Richardson Shaffer contact lens was used. Electroretinography by Karpe's method (Karpe 1962) was performed in all cases.

Fluorescein angiography (TAG) of the macula and perimacular area was performed on 9 children under general anaesthesia. 1.5 cc of 10% Na fluorescein was rapidly injected into a cubital vein. The Zeiss fundus camera and a connected Robot recorder device were used. A Bird Atomic interference filter no. 4 was used for excitation and a Kodak Wratten no. 15 filter for absorption. The child was in a recumbent position lying on one side. The fundus photography was performed in the usual way.

Ophthalmological Findings

The ophthalmological findings have been summarized in Table I. Visual deterioration was present in all children but one namely the youngest a 20 month

Patient	Age (years/ months)	Vision	Motility Squint	Optic disc	Fundus as seen at		ERG
					Macula	Periphery	
F CK	1/6	Follows object blind	Coordinated	Atrophic	Normal	Hypopigmented	Abolished
M JM	9/11	Light perception	Incoordinated	Atrophic	Brownish	Hypopigmented	Abolished
M PK	1/11	Light perception	Coord noted	Atrophic	Brownish gray	hypopigmented	Abolished
	1/8	Light perception	Exotropia	Atrophic?	Reduced lustre	Hypopigmented	Abolished
FV BH	2/2	Light perception	Exotropia	Atrophic	Brownish		Abolished
					Reduced lustre	Hypopigmented	
M PV	1/11	Blind	Incoordinated	Atrophic	Brownish	Hypopigmented	Abolished
					Reduced lustre		
F AS	1/11	Light perception	Exotropia	Atrophic	Brownish	Hypopigmented	Abolished
					Reduced lustre		
M HQ	2/11	Blind	Exotropia	Atrophic	Brownish	Hypopigmented	Abolished
					Reduced lustre		
F RS	3	Blind	Incoordinated	Atrophic	Brownish	Hypopigmented	Abolished
			Exotropia		Reduced lustre		
F TS	2/11	Blind	Incoordinated	Atrophic	Brownish	Hypopigmented	Abolished
M PP	3/6	Blind	Incoordinated	Atrophic	Not distinguish- able	Hypopigmented	Abolished
M PP	4	Blind	Incoordinated	Atrophic	Not distinguish- able	Hypopigmented	Abolished
M TK	1/10	Light perception	Coordinated	Atrophic?	Brownish	Increased lustre	Abolished
F MK	2	Light perception	Coordinated	Normal?	Brownish	Periphery Hypopigmented	Abolished
F MM	9/9	Light perception	Exotropia	Atrophic	Brownish	Hypopigmented	Abolished
M KH	2	Blind	Incoordinated	Atrophic	Brownish	Hypopigmented	Abolished
M VV	9/4	Blind	Incoordinated	Atrophic	Brownish	Hypopigmented	Abolished

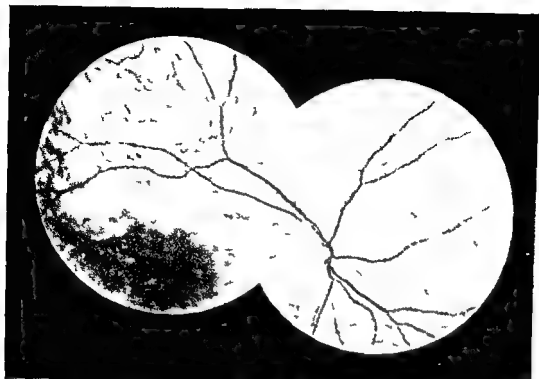


Fig 1

Retina of patient M JM with light perception and reduced pupillary response Hypo pigmentation of fundus yellowish atrophic disc and narrow retinal vessels Brownish patchy macula



Fig 2

Retina of a blind 4 year old boy with yellowish atrophic optic disc dystrophic retina especially of the macula

old child who followed a moving object and had normal pupillary reactions. Seven children were classified as having light perception. 8 were classified as blind. These children had an absent direct pupillary reaction. One child was examined twice. When first seen she followed a moving object. One year and 5 months later she was blind. Disturbed eye motility was present in 15 children, mainly exotropia and/or incoordinated eye movements. The cornea and the lens were clear in all cases.

The fundus was considered normal only once in the youngest child examined. The typical finding (Fig. 1) was hypopigmentation of the fundus with clearly visible choroidal vessels, brownish colour of the macula and an increased lustre of the retina. No pigment aggregation of the fundus periphery was present. The late funduscopic picture was dominated by retinal dystrophy especially of the macula (Fig. 2), optic atrophy, narrowing of vessels but no distinct pigment aggregation of the periphery. The electroretinogram was abolished in all cases.

The essential features of the FAG were narrowing of the retinal vessels, progressive disarrangement and thinning of the pigment epithelium and defects and aggregation of pigment in the macula. The normally densely pigmented macula showed patchy and ringlike defects (Fig. 3). The retinal vessels were narrow.

Discussion

Zeman & Dyken (1969) emphasized that the group of amaurotic family idiocy is heterogeneous and at least two more severe conditions, gangliosidosis and neuronal ceroid lipofuscinosis (NCL, the Batten Vogt syndrome) can be separated from it. No specific abnormalities in the gangliosid metabolism have been detected in NCL patients (Zeman et al. 1969).

In the group of NCL Zeman et al. (1970) classified separately the rapid course of Jansky-Bielschowsky, the slowly progressive form of Spielmeyer-Sjoegren and the adult type of Kufs. However, Haltia et al. (1973) and Santavuori et al. (1973) emphasized that there is still a fourth group belonging to the NCL family. In the NCL group there is a primary involvement of the receptor and the pigment epithelium instead of involvement of the ganglion cell layer as in gangliosidosis.

In the early onset of NCL the visual failure begins more or less simultaneously with the neurological signs leading rapidly to blindness. In the youngest age group there were five children exhibiting reaction to light. However, in a control examination 1-11/2 years later no light perception was observed. This

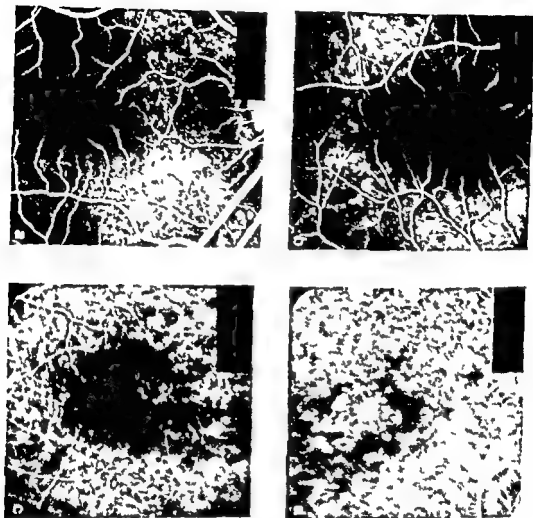


Fig 3

Fluorescein angiogram in a normal child and different stages of neuronal ceroid lipofuscinosis of early onset

a) FAG pattern of normal 3 year old child b) narrow retinal vessels and increased choroidal glow indicating thinning of the pigment epithelium in a 1/10 year old boy with neuronal ceroid lipofuscinosis c) the pattern of a 2 year old boy shows a more advanced case with markedly narrowed retinal vessels and a pathologic patchy macula d) advanced changes in a 4 year old boy with extremely narrow retinal vessels hardly visible in the FAG almost complete absence of pigment in the macula and optic atrophy

is in contrast to gangliosidosis in which pupillary light reflex remains normal (Copenhaver et al 1960 Menkes et al 1971). Deterioration of the visual function was rapidly progressive. The children were practically blind at the age of two and completely blind at the age of three. Disturbance of ocular motility was secondary to the diminished vision. Only one child showed normal ocular motility when seen in the early phase of the disease. In this phase FRG and FAG contribute to the exact diagnosis. In this respect the entity differs from the so called Jansky Bielschowsky disease in which deterioration of vision is said to be late and unimportant (Zeman et al 1970 Menkes et al 1971).

Electroretinography was performed in all cases in order to clarify the amount of retinal changes. Mawmence & Emery (1972) localize the pathologic changes of NCL to the nerve fibre ganglion cell layer. The electroretinographic finding and fluorescein angiography clearly indicate the receptor cell layer and the pigment epithelium to be primarily affected. The electroretinogram arises from the outer retinal layers from the area including the bipolar cell layer and the receptors. The ganglion cell and nerve fibre layer do not contribute. The ERG was abolished in NCL in contrast with the normal ERG seen in the gangliosidosis (Cogan 1964). An electroretinographic investigation was performed by Copenhaver & Goodman (1960) in late infantile and juvenile amaurotic idiocy. The electroretinogram was absent or markedly depressed in their cases. The ERG of our series was abolished in all cases examined and this seems to be an important differential diagnostic method in children with progressive encephalopathy.

The fluorescein angiographic findings included signs of retinal dystrophy and progressive changes in the pigment epithelium especially of the macula. The ganglion cell layer and nerve fibre layer seem to be affected early as seen in the narrowing of retinal vessels and optic atrophy. Therefore fluorescein angiography performed during the same anaesthesia as the FRG is also important for the early diagnosis.

Summary

Ophthalmological findings in neuronal ceroid lipofuscinosis of early onset are delineated.

Sixteen children (aged 2 months to 4 years) were examined ophthalmologically. Neurologic signs preceded ocular symptoms. Progressive deterioration of vision and incoordinated eye movements were typical functional disturbances. Hypopigmentation of the fundus, progressive changes of the macula and optic atrophy were typical. The electroretinogram was abolished in all cases, clearly

Table II

Patient	Age (years/ months)	Vision	Motility squint	Optic disc	Fundus appearance		IRG Not examined
					Macula	Periphery	
M TR	7/9	Light perception	Coordinated	Atrophic	Brownish gray	Hypopigmentated	Not examined
M JL	5/9	Light perception	Incoordinated	Atrophic	Reduced lustre	Hypopigmentated	Abolished
M JS	1/8	Light perception	Isotrophia	Atrophic	Browning		Abolished
F IS	7/6	Blind	Incoordinated	Atrophic	Reduced lustre	Hypopigmentation	Abolished
					Browning		
M AS	7/11	Blind	Incoordinated	Atrophic	Reduced lustre	Hypopigmentation	Abolished
M TR	2/9	Light perception	Incoordinated	Atrophic ?	Not distinguishable	Hypopigmentation	Abolished
M TR	2/1	Light perception	Coordinated	Normal ?	Normal		Abolished
M MA	1	Light perception follows moving object	Coordinated	Normal ?	Browning		Abolished
F AS	4	Blind	Incoordinated	Atrophic	Dystrophic		Not examined
F SS	7/7	Blind	Incoordinated	Atrophic	Dystrophic		Not examined
F JS	6/7	Light perception	Incoordinated	Atrophic	Dystrophic	Hypopigmentated	Not examined
F SJ	3/2	Light perception	Incoordinated	Atrophic	Brownish		Abolished
M II	1/8	Blind	Incoordinated	Atrophic	Dystrophic		Not examined
F III	1/6						
F MI	5/6	Light perception	Incoordinated	Atrophic	Dystrophic	Hypopigmentated	Abolished
F MI	7/4	Blind	Incoordinated	Atrophic	Dystrophic		Abolished
F TI	3/7	Light perception	Incoordinated	Atrophic	Dystrophic	Hypopigmentated	Abolished
M VV	2/3	Light perception	Coordinated	Atrophic	Reduced lustre	Hypopigmentated	Abolished
M JI	3	Blind	Incoordinated	Atrophic	Dystrophic		Not examined

indicating that the primary defect was in the receptor cell layer and pigment epithelium of the retina

Fluorescein angiography supported these findings and seems to be an important diagnostic method in the differential diagnosis of progressive encephalopathy

Addendum

Since the report on the present investigation was accepted for publication in December 1972 19 additional cases (Table II) have been diagnosed. The essential ophthalmological findings of progressive retinal dystrophy and an abolished ERC were confirmed. The fluorescein angiogram showed changes of the pigment epithelium and the ERG was abolished before manifestation of clinical signs in our youngest patient (MA 12 months). The findings confirm that the primary ocular defect lies in the receptor cells and the pigment epithelium.

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LENTICULAR AND RETINAL CHANGES SECONDARY TO MICROWAVE EXPOSURE

BY

E. AURELL AND B. TENGROTH

The cataractogenic effect of exposure to microwaves has been reported by several authors. Effects on the central nervous system also have been discussed. Whether the effect is thermal in origin or nonthermal is not known. In this paper the authors show that in a factory where radar and other microwave equipment was tested, an overrepresentation of lens opacities could be observed in personnel in the lower age groups. Furthermore, it was noted that changes in the retina resembling chorioretinal scars were present in a significant number of workers.

Key words: microwaves - electronic oven - radar - radio frequency - cataract - chorioretinitis - radiation - lens opacities - retinal lesions

During the past quarter century there has been marked development and increased utilization of devices and equipment for industrial and medical applications as well as for military use that emit a large variety of non ionizing radiant energy. Microwaves have come into use primarily in the military field but also as diathermy in medical therapy and for consumer's use in cooking. Today microwave emitters are widespread. The electromagnetic radiation characterized as microwaves has a wavelength between 0.3 mm and 300 cm corresponding to 10^9 - 10^1 Hz. The microwave energy can be propagated either pulsed or as a continuous wave (CW).

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Where the microwaves are absorbed they give an increased kinetic energy to the molecules exposed which will increase the possibility of collisions between molecules and hence result in increased temperature in the entire material

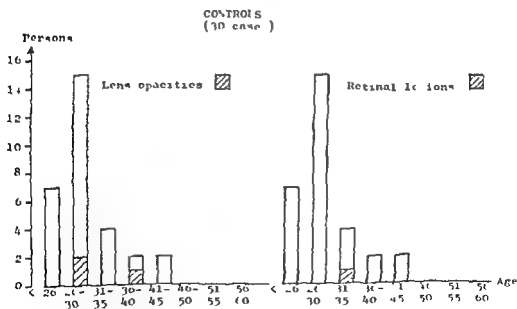
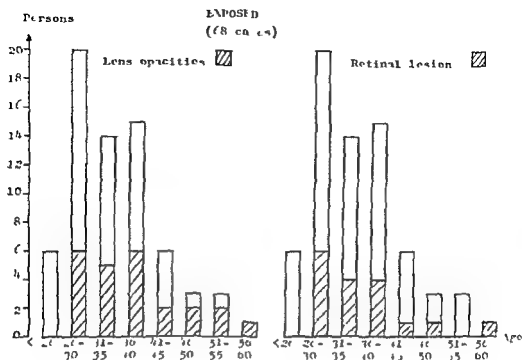
The biological effect of microwaves has been very thoroughly investigated in many places but especially in the Triservice Program (Michaelson 1941 Michaelson et al 1967 Pattishall 1957 Pattishall et al 1958 Peyton 1961 Susskind 1959 Cleary 1940 Michaelson 1971 Milroy et al 1971 Roth 1968)

It is generally agreed that mostly the effect of microwaves on tissue is of thermal origin. However non thermal effects have been suggested and there is still a great deal of controversy on this subject (Michaelson et al 1967 Cleary 1940 Michaelson 1941 Milroy et al 1971 Roth 1968 Michaelson et al 1941 Dodge et al 1966 Presman 1965 Presman 1940 Turner 1962 Dodge 1965 Gordon 1960 Tolgskaya et al 1960 Osipov 1965 Livshits 1957 Livshits 1967 Gorodetskaya 1963 Gorodetskaya 1964 Levorkyan 1948 Levitina 1964 Lobanova 1960 Minecki 1961 Presman et al 1962 Presman & Levitina 1967 a b Presman et al 1961 Sadchikova et al 1958 Subbota 1957 Tyagin 1957 Vavala 1968)

One of the most investigated fields concerning the pathological effects of microwaves is the denaturation of lens proteins resulting in lens opacities - cataract (Carpenter 1959 Carpenter & van Ummeren 1968 Richardson Duane & Hines 1948 Zaret 1964 Appleton & McCrossan 1972)

General effects on the central nervous system i.e. headache and nausea have been reported from the USSR but it is still a matter of dispute as to whether these symptoms are secondary to temperature increase in the organism or direct nonthermal effects on the nervous tissues

The experimental work cited above has resulted in recommendations of maximum permissible exposure (MPE) of 10 mW/cm^2 a figure used in the Western world. The figure presented by the Soviet Union is much lower namely 0.01 mW/cm^2 . Most industries or military organisations involved in microwave work are recommended to make yearly checks on their personnel especially their eyes. In one of the industries working with radar equipment such check ups started quite recently. The preliminary findings were rather surprising in two ways: first the frequency of significant lens opacities in the younger age group were greater than expected and second retinal lesions in the paramacular and macular region were registered in a number of cases with decrease in vision in two cases. As retinal lesions have never been reported in the literature as far as we know an epidemiological study was performed in order to discover whether the above mentioned findings had any significance.



Material

A total of 98 employers in an electronic industry developing radar equipment were investigated. Of these 68 had been exposed to microwaves for a certain period or were still working in this field. This group could be divided into persons testing radar equipment and measuring microwave radiations from different chlystrons and persons from the experimental laboratories. A control group of 30 persons from the same industry had never been exposed to microwave radiation as far as was known.

Material and Methods

Two eye specialists made a careful independent eye examination of all above mentioned personnel without any knowledge of their occupation or microwave exposure.

The examination included refraction and determination of visual acuity, a study of the optical medias with the aid of a corneal microscope and slit lamp in complete mydriasis and an ophthalmoscopic study of the retina.

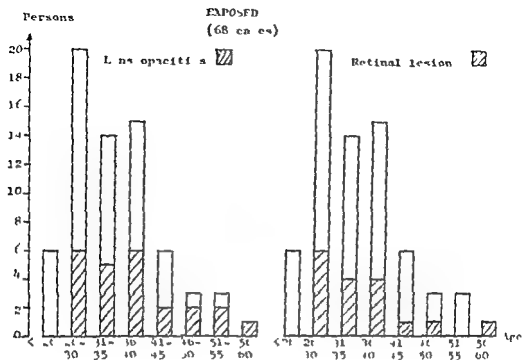
Definitions

Only opacities of a diameter of more than 0.5 mm or a large concentration of smaller opacities in the subcortical region were taken into account. Very small opacities spread out in the lens were not registered. The opacities should be detectable also in the ophthalmoscopic media examination.

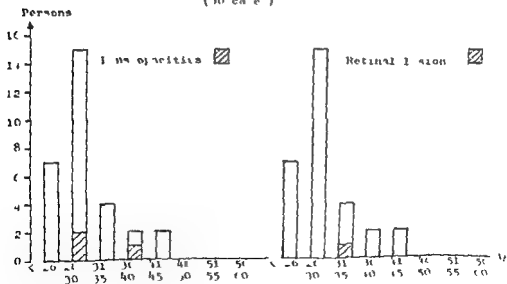
Retinal lesions were looked for only in the central part of the fundus and were characterized by their resemblance to chorioretinal scars after inflammatory reactions. Small yellow changes in this region were also observed and registered but were not classified as lesions of significant importance.

Result

As seen in the diagram the number of exposed subjects with lens opacities is high even in the younger age groups. In the higher age group - over 41 years - it is impossible to separate lens opacities due to microwave exposure



CONTROLS
(70 cases)



be stressed and further experiments have to be carried out as damage to a nervous tissue such as the retina suggests that similar changes might appear in other nervous tissue after exposure to microwaves

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from a senile cataract because no controls older than 41 years were examined.

Retinal lesions hitherto never reported were also frequent. That only one case was found in the control group makes the exposed group significantly different. Dividing the group of exposed personnel according to their tasks (testing personnel, laboratory personnel) a concentration of lens- and retinal lesions is observed in the former.

Discussion

It is of great interest that eye lesions both lenticular and retinal found in this material are significantly higher in the group of persons belonging to the test group than the persons working in the laboratories. It is difficult to draw conclusions as to which kind of work entails the most risk, but one knows that the personnel testing the equipment for measuring radiation are more liable to exposure from higher power levels than others, i.e. laboratory personnel. This is of importance as the MPE of 10 mW/cm² might be too high a figure - a comparison with the Soviet figures suggests this. Another explanation is that the eye lesions observed are due to leakages from the equipment or carelessness on the part of the personnel. As we have a concentration of damaged persons in a certain exposed group the MPE probably is sufficient and the other reasons are more likely.

The retinal lesions observed have been briefly reported by the authors previously (Aurell & Tengroth 1972). Since then a message from a Polish scientist (Czerski, pers. communication) revealed that in a very recent study initiated by our findings similar retinal lesions were observed in personnel exposed to microwaves which confirms our observations.

The pathogenesis behind the retinal lesions is very obscure. The transmission properties of microwaves in biological tissues do not explain why certain areas in the retina should be changed as a result of thermal effects. The change in dielectric constants in the different layers of the retina might give an increase in intensity of 3 to 4 times in the layers but this seems too slight to explain the damage.

Whether nonthermal radiation effects cause these changes is of course not known. Further experimental and theoretical work has to be carried out in order to find the explanation. The most important findings reported here are the retinal lesions as these lesions have resulted in a decrease of vision in two cases. In no known case have the lens opacities resulted in a comparable loss of vision. In the future a careful examination of the eye fundus has to

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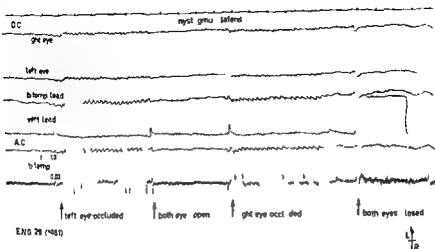


Fig 1

Latent nystagmus on occlusion of the left eye nystagmus appears to the right and on occlusion of the right eye nystagmus appears to the left when both eyes are open or closed there is no nystagmus

mind it was quite curious to repeatedly find a latent nystagmus in monocular fixation with a blind eye or even with an eye prosthesis (Fig 2) This does not agree with theories attempting to explain latent nystagmus by assuming anomalies of fixation reflexes Kornhuber (1961) assumed that a disturbance of fixation reflexes cannot explain the syndrome of latent nystagmus He considers latent nystagmus to be the result of a disorder in the centres of the brain stem which regulate oculomotor coordination

Observation of a case of latent nystagmus which contrary to all afferent theories also occurred during monocular gaze intention following acoustic stimulation in complete darkness (Kornhuber 1961 van Vliet 1963) led us to investigate the syndrome of latent nystagmus with regard to the above mentioned problem

Material

During a period of 55 years 83 cases of latent nystagmus were examined Twenty one cases were referred to us in the course of a detailed examination of institutionalized partially sighted children (van Vliet 1964) and 20 out patients from the Eye Clinic at Rotterdam were referred to us with nystagmus

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ON THE CENTRAL MECHANISM OF LATENT NYSTAGMUS

BY

A G M van VLIET

The eye movements of patients with latent nystagmus were recorded during monocular gaze intention following acoustic stimulation in complete darkness and in a series of experiments with the aid of the kryptopic pseudoscope of Lwald. It appears to be the intention of looking with one eye which elicits latent nystagmus. Moreover, it can be shown that the moment of appearance and the direction of the nystagmus are determined not by the illuminated retina but by the act of pointing an object with one eye. The preponderance of motor over sensory factors and especially of intentional motor behaviour is clearly demonstrated. The possible central mechanism of latent nystagmus is discussed.

Key words: latent nystagmus - congenital nystagmus - monocular visual attention - monocular optokinetic stimulation - kryptopic pseudoscope of Lwald - fixation reflex - directional preponderance of gaze tone

Latent nystagmus is a condition in which nystagmus not normally present with both eyes open or closed becomes manifest on occlusion of one eye (Fig. 1). This nystagmus occurs both in the occluded and in the unoccluded eye with the rapid component towards the side of the open eye.

Most theories postulate the presence of a unilateral retinal stimulus as a necessary condition for the evocation of latent nystagmus (Fromaget 1912; van der Hoeve 1917; Kestenbaum 1921; Roelofs 1928). With these theories in

The following modifications were used. Recordings were made with an eight channel Offner Type T Electro encephalograph consisting of 4 D.C. amplifiers which allow an accurate recording of the true position of each eye in both the horizontal and vertical plane and 4 A.C. amplifiers (time constant 0.03) which allow the simultaneous recording of the speed of the eye movements (the so called nystagmograph) and of the angular velocity of the optokinetic stimulus. The leads were arranged in such a way that an eye movement to the left was recorded as an upward deflection and vice versa.

Passive optokinetic nystagmus was examined by means of an apparatus similar to that used by ter Braak & van Vliet (1963). For the examination of active optokinetic nystagmus an apparatus has been devised which imitates the effect of the movement of a strip of white paper 16 cm long and 8.5 cm wide. The strip which has a pattern of black lines of the same width (1 cm) as the intermediate white spaces moves with constant angular velocity of approximately 17 /sec. All patients were examined for optokinetic nystagmus with both binocular and monocular vision. Asymmetry (e.g. of the angular velocity of the slow phase of optokinetic nystagmus or of the total amplitude of the first postrotatory nystagmus) was calculated by means of the following formula

$$D = \frac{L - R}{L + R} \times 100\%$$

We assumed a difference of 20% in angular velocity (/sec) or in total amplitude between the nystagmus to the right and that to the left to be the marginal value.

As the above mentioned observation of latent nystagmus occurred in total darkness the eye movements in all these patients were recorded during monocular visual attention elicited by acoustic stimuli in the dark. For this purpose the following experiment was chosen. The patient closed both eyes and in addition covered one closed eye with the ipsilateral hand. After that the room was darkened and the patient was ordered to open the uncovered eye and to try and fix a sound elicited by the examiner who continuously encouraged the patient to do his utmost to discern the examiner. The eye movements were registered by means of electronystagmography.

Finally an investigation was carried out with the aid of Ewald katoptric pseudoscope (Fig 3). With this instrument the visual fields of the two eyes are interchanged by means of double reflection through an arrangement of four mirrors as shown in (Fig 4). Whilst the patient believes that he excludes the rays to his right eye by covering the right aperture he actually covers the rays to his left eye and vice versa.

LATENT NYSTAGMUS ■ MONOCULAR FIXATION WITH AN EYE-PROSTHESIS

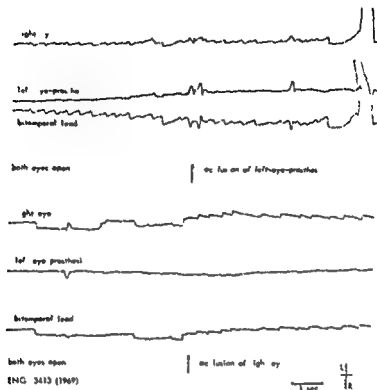


Fig 2

There is nystagmus to the right both with open eyes and on occlusion of the left eye prosthesis. On occlusion of the right eye however, i.e. fixation with the left eye prosthesis, nystagmus to the left appears and for obvious reasons occurs only in the occluded right eye.

and amblyopia. Another 22 cases were out patients and 11 were in patients of the Department of Neurology of the Municipal Hospital "Dijkzigt" in Rotterdam and 9 patients seen by private neurologists were referred to us with nystagmus which as a rule had already been diagnosed as belonging to the category of latent or congenital nystagmus.

Methods

Electronystagmography was performed on all patients. In addition the patients underwent routine ophthalmological and neurological examinations.

For the recording and evaluation of nystagmus use was made of the electro-nystagmographical method described by Jung (1953).

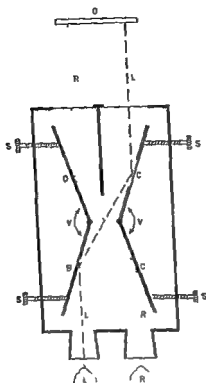


Fig 4

Course of the rays of light in the katoptic pseudoscope

inversion of the optokinetic nystagmus (with fast phase towards the fixing eye) when the stimulating movement was directed towards the fixing eye. On binocular stimulation disturbances of horizontal optokinetic nystagmus are more frequent (62 cases 13%) than those of vertical optokinetic nystagmus (44 cases 53%).

In the 83 patients examined when monocular visual attention was aroused by acoustic stimuli straight ahead in the dark the results were as follows

Bilateral latent nystagmus in darkness	
with bilateral occurrence by light	39 = 47%
with unilateral occurrence by light	3 = 3%
Unilateral latent nystagmus in darkness	
with bilateral occurrence by light	19 = 23%
with unilateral occurrence by light	
in same direction	4 = 5%
in opposite direction	1 = 1%
No latent nystagmus in darkness	18 = 22%
	83 = 100%

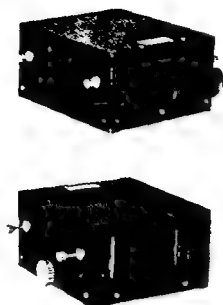


Fig 3
The Ewald koptoe pseudoscope

Results

Out of 83 persons 53 (64 %) were found to have the typical syndrome of latent nystagmus 28 (34 %) of whom showed no nystagmus 3 (4 %) only pendular nystagmus on binocular fixation and 22 (26 %) jerk nystagmus on alternating monocular fixation when both eyes were open The remaining cases of latent nystagmus were atypical in that nystagmus of the jerking type was already present in the central position when both eyes were open Eighteen cases (22 %) had a pendular nystagmus in binocular vision and 52 (63 %) had a gaze direction nystagmus Out of 77 cases 46 (60 %) had spontaneous nystagmus with closed eyes while there was pathological directional preponderance in 38 (55 %) out of 69 persons In the 28 cases in which spontaneous nystagmus with closed eyes coincided with pathological directional preponderance both the spontaneous nystagmus and the directional preponderance were directed in the same way in 27 cases

Latent nystagmus is characterized by a typical disturbance of nystagmus on monocular optokinetic stimulation In almost all cases (50 = 96 %) asymmetry was found to favour the direction of the latent nystagmus which varied from inhibition of the optokinetic nystagmus toward the occluded eye to

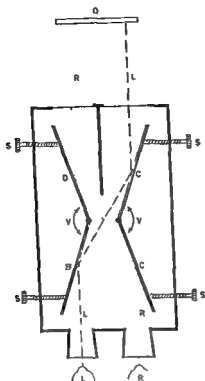


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in opposite direction	1 = 1%
No latent nystagmus in darkness	19 = 29%
	<hr/> 83 = 100%

Out of 83 persons thus examined, 65 (78%) showed latent nystagmus in complete darkness (Fig 5). In those cases in which there was no latent nystagmus in monocular fixation of a sound in the dark it was doubtful whether the patient had been able to give enough attention especially as some jerks occasionally occurred when the test was begun but not on repetition.

In the cases with latent nystagmus in monocular fixation of a sound in the dark, it appeared that the extent to which nystagmus occurs depends on the sharpness with which the acoustic perception is transformed into the intention to look. In other words latent nystagmus can be elicited by monocular visual attention.

This concept of the mechanism of latent nystagmus would become more convincing if latent nystagmus could be elicited by the intention to monocular fixation not only independently of visual afferents in the fixing eye but also if the non fixing eye received a retinal stimulus as well.

Accordingly an investigation was carried out in 11 patients with the aid of the Iwald katoptric pseudoscope. In seven out of 11 patients it appeared that latent nystagmus could be elicited. The rapid component of this type of nystagmus is directed towards the side of the instrument which remains un-

latent nystagmus in total darkness

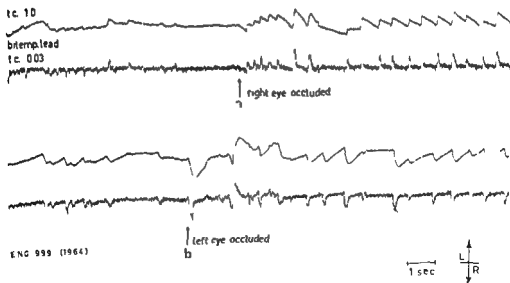


Fig 5

At point a the right eye is occluded and acoustic stimuli are fixed with the left eye in complete darkness. A latent nystagmus to the left appears. At point b the left eye is occluded. The slight nystagmus to the right is clearly increased.

investigation with the katoptric pseudoscope of avnold

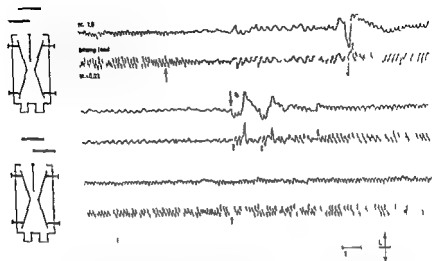


Fig 6

This patient has nystagmus to the left at point a the patient is asked to occlude the left aperture of the katoptric pseudoscope with the left hand nystagmus to the right occurs At point b the left hand is removed the nystagmus to the right disappears and the nystagmus to the left returns

At c the patient is asked to occlude the right aperture of the pseudoscope with his right hand. The nystagmus to the left increases by 50% even though the right eye receives retinal stimuli and the left is deprived of them

obstructed i.e. in the direction of the eye which receives no retinal stimulus (Fig 6)

On the other hand there was no nystagmus when the examiner was secretly covering one aperture of the pseudoscope From this it may be concluded that the intention to look with one eye determines the evocation of latent nystagmus even if this eye does not receive retinal stimuli and the other non fixing eye does

Discussion

The above observations prove that latent nystagmus can be independent of retinal stimuli Therefore they are an argument against exclusively afferent theories of latent nystagmus It appears to be the intention of looking with one eye which elicits latent nystagmus

Under normal circumstances looking means maintaining fixation on cer

tain favoured objects (ter Braak 1957) It may be assumed that the fixation reflex then becomes facilitated towards the movement of the favoured object Results of the examination of latent nystagmus in total darkness make the existence of something like "looking without a visual object" plausible The intention to look with both eyes does not result in manifest nystagmus

On the contrary, the intention to "look with one eye" leads to nystagmus in the direction of the looking eye This suggests that the above mentioned facilitation which is supposed to exist when "real" visual objects are looked at could depend on an asymmetrical increase in gaze tone which in case of latent nystagmus results in nystagmus This hypothesis is supported by the reactions of persons with latent nystagmus to monocular optokinetic stimulation In almost all cases (96%) asymmetry was found in favour of the direction of the latent nystagmus which varied from inhibition of the optokinetic nystagmus towards the occluded eye to inversion of the optokinetic nystagmus when the stimulating movement was directed towards the fixing eye Thus "looking with one eye" would imply at least in the presence of latent nystagmus an asymmetrical increase in tone of the gaze innervation resulting in either facilitation or inhibition of certain fixation reflexes

It is well known that a lesion of one hemisphere may cause a transitory asymmetry of tone in the gaze innervation resulting in the so called cerebral nystagmus Nystagmus of this kind is directed towards the focus and may be ascribed to temporary preponderance of the intact hemisphere If therefore latent nystagmus in monocular vision is ascribed to preponderance of the gaze innervation of one hemisphere it follows that looking with only the right eye must bring about a preponderance of the left hemisphere The predominant relationship of each eye to the contra lateral hemisphere brings to mind the phylogenetically older situation existing in the rabbit in which all optic impulses are conducted to the contra lateral hemisphere The only hint of this situation in man could be the temporal monocular field of vision In our opinion the directional preponderance of gaze tone brought about by the intention to "look with one eye" must depend on a cortical mechanism

The pathological substrate of latent nystagmus must be found in brain stem centres which normally compensate for the asymmetrical cortical influence Various oculomotor anomalies frequently accompanying latent nystagmus support this point of view Among these anomalies are directional preponderance, spontaneous nystagmus with closed eyes, dissociated gaze direction, nystagmus and severely disturbed optokinetic nystagmus

The asymmetrical cortical influence on horizontal gaze tone induced by the intention to "look with one eye" could become manifest by defective compensation from the pathological brain stem centres

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NYSTAGMOGRAPHICAL STUDIES IN ÅLAND EYE DISEASE

BY

A G M van VLIET P J WAARDENBURG¹ H FORSIUS
and A W ERIKSSON

An extensive electronystagmographical examination was made of 25 members of a family with Åland eye disease (Forsius Eriksson syndrome). It appears that the nystagmus belongs to the syndrome of latent nystagmus. Out of seven investigated male subjects with Åland eye disease five showed classical latent nystagmus and two had slight manifestations of latent nystagmus. Of nine investigated female subjects only two revealed a very slight latent nystagmus. According to our studies we can postulate two modes by which latent nystagmus could have been inherited in this family:

- (1) an X-chromosomal dominant type of transmission with decreased or lack of penetrance in a number of female carriers
- (2) a recessive X-chromosomal transmission with slight nystagmus as a sign of heterozygosity in the female carriers

The combination of latent nystagmus with the X-chromosomal Åland eye disease may be explained by pleiotropic gene action.

Key words: Åland eye disease - extra ocular nystagmus - hereditary nystagmus - latent nystagmus - monocular visual attention - inheritance of nystagmus - heredity

¹⁾ Dr P J Waardenburg was formerly Lecturer in Medical Genetics at Utrecht and Leiden Universities

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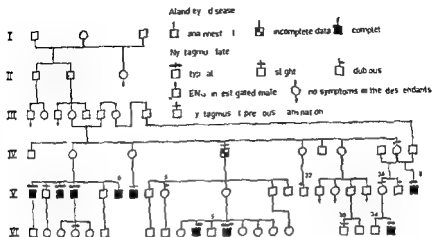


Fig 1
Pedigree of the family with Åland eye disease

The aim of the present paper is to summarize a rather extensive electronystagmographical analysis of the eye movements in a family with an X chromosomal eye syndrome the Forsius Eriksson syndrome (1964). This syndrome is characterized by a combination of poor sight, axial myopia, regular astigmatism, hypoplasia and pigmentary deficiency of the fundus, defective dark adaptation and nystagmus (Waardenburg et al 1969, Eriksson et al 1969). At first the nystagmus was explained by the poor sight and the foveal hypoplasia, with the exception of a female carrier (IV 15) and her daughter (V 36) both of whom had normal vision. Here the nystagmus was thought to be of extraocular origin and probably mere chance. However, inspection of the previous examinations of 1963, 1966 and 1967 strongly indicated to one of us (van Vliet) that the nystagmus was of extraocular origin in all members of the pedigree. Therefore, in 1969 an extensive electronystagmographical examination of 105 members of this family was made (Fig 1).

Methods

For the recording and evaluation of nystagmus the electronystagmographical method was used as described by Jung (1953). The following modifications were made. Recordings were made with a portable one channel van Gogh Nystagmograph consisting of an AC amplifier with a time constant of 8 sec.

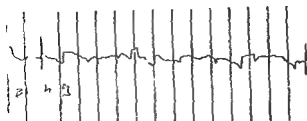
which allows fairly accurate recording of the true position of the eyes in the horizontal plane when the electrodes are placed on the outer canthus of each eye. The leads were arranged in such a way that an eye movement to the left was recorded as an upward deflection and vice versa.

Results

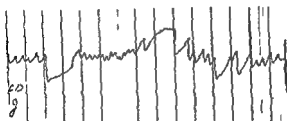
The results were as follows. Out of 25 persons four male subjects (V 1 V 5 V 6 and VI 16) had the typical syndrome of latent nystagmus presenting a jerky nystagmus when either eye was occluded with the fast component to the side of the open eye but showing no gross nystagmus when both eyes were open (Fig. 2).

In the adult male V 6 gross alternating jerky nystagmus was present with both eyes open and was made more pronounced by occlusion of either eye. The boy VI 14 showed gross jerky nystagmus to the left with both eyes open which was inhibited by occlusion of the left eye. Besides other criteria the inhibition of a manifest nystagmus on occlusion of the homonymous eye (that is homonymous to the fast phase of the nystagmus) points to the syndrome of latent nystagmus. Therefore the boy VI 14 had a unilateral latent nystagmus to the left which had become manifest. Pendular nystagmus in binocular fixation found in these five male subjects on former examinations (Forsius et al 1964) is not unusual in the syndrome of latent nystagmus (van Vliet 1973). This is also true for the gaze direction nystagmus which was present in three of the above mentioned male subjects (V 1 VI 14 and VI 16).

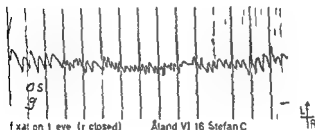
Mild cases of latent nystagmus often are overlooked. These cases can easily be detected by ophthalmoscopy especially with the Thorner ophthalmoscope during studies of optokinetic nystagmus with monocular stimulation or during monocular gaze intention following acoustic stimulation in complete darkness. With (Thorner) ophthalmoscopy nystagmus in the direction of the fixating eye was present bilaterally in two other males (V 39 and VI 35) and one girl (VI 7) and only unilaterally in two males (V 22 and V 37) and one female (V 15). In the case of unilateral nystagmus with ophthalmoscopy it is very difficult to differentiate between latent and other nystagmus and therefore they are considered as dubious latent nystagmus. Latent nystagmus is characterized by a typical disturbance of nystagmus on monocular optokinetic stimulation (van Vliet 1973 and Fig. 3). Besides in the five typical cases of latent nystagmus an asymmetry of optokinetic nystagmus favouring the direction of the latent nystagmus was found in both males who only showed bilateral



with eyes open



fixation r eye (l closed)



fixation l eye (r closed)

Åland VI 16 Stefan C

Fig. 2

Latent nystagmus of an 11 year old boy

slight latent nystagmus by ophthalmoscopy in V 38 there was also found an asymmetry favouring the direction of latent nystagmus by monocular optokinetic stimulation in the vertical direction in VI 35 only by horizontal optokinetic stimulation of the left eye

The girl (VI 7) with bilateral slight latent nystagmus detected by ophthalmoscopy showed latent nystagmus to the left in total darkness when monocular visual attention of the left eye was elicited by acoustic stimuli from directly ahead in the dark. So the cases V 38 VI 35 and VI 7 can be considered as latent nystagmus on the basis of at least two criteria

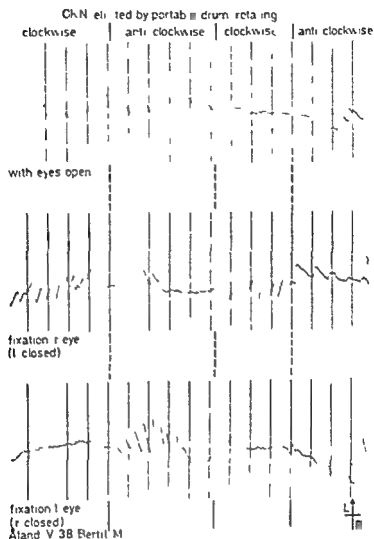


Fig 3

Asymmetry of monocular evoked optokinetic nystagmus favouring the direction of the open eye

The female member of the pedigree IV 15 had a rather symmetrical gaze direction nystagmus. Disappearance of this gaze direction nystagmus by occlusion of the abducted eye seems to point to a latent nystagmus. The typical disturbance of nystagmus on monocular optokinetic stimulation was present only in the right eye but the strong directional preponderance to the right might have levelled the asymmetry of the optokinetic nystagmus with monocular stimulation of the left eye.

No.	Sex	Nystagmus reaction (to → to L ← to R ← to eye) (sec)							Remarks
		Open eyes	One eye	Thermal eye	Latent eye	Monocular eye	One eye	Open eyes	
IV 1	♀			↖ ↗	↖ ↗	↖ ↗		↖ ↗	lat comp. of gaze yet d. at prepond. to R.
V 1	♂	very L. n.	2.5/ 4/	↖ ↗	fast fast	↖ ↗		↖ ↗	
V 3	♂		5/ 2/	↖ ↗		↖ ↗		5/	
V 4	♂	4 15	21 18	↖ ↗		↖ ↗	6 17	III	
V 11	♂			↖ ↗					d. at pre pond to L.
V 15	♀			↖ ↗					
V 37	♂			↖ ↗		↖ ↗			eye to L. in vert. c. inst. on OS
V 39	♂			↖ ↗				3/	
VI 7	♀			↖ ↗				17/	
VI 14	♂	18	6 10	↖ ↗	slow stage 18	↖ ↗	long	17	
VI 16	♂		27 27	↖ ↗	35	↖ ↗	4 1	28	
VI 33	♂			↖ ↗	2	↖ ↗	2	4	1 comp. of gaze nyst

Fig 4
Summary of the nystagmographical results in Aland eye disease

Thus we have enough criteria to consider that in addition to the other patients the nystagmus of IV 15 also has the syndrome of latent nystagmus. Summarizing we found (Figs 1 and 4)

- 1 A typical syndrome of latent nystagmus in four male subjects (V 1 V 5 V 6 and VI 16)
- 2 A unilateral expression of the syndrome of latent nystagmus in one boy (VI 14)
- 3 A slight form of the syndrome of latent nystagmus only detectable with ophthalmoscopy by monocular optokinetic stimulation or during monocular gaze intention in complete darkness in two male (V 38 and VI 35) and two female subjects (IV 15 and VI 7)
- 4 Finally there were two males (V 22 and V 37) and one female (V 15) with only a unilateral nystagmus on ophthalmoscopy this is not in itself diagnostic for the latent character of the nystagmus but in this pedigree it is highly suggestive of this disease

Discussion

The nystagmus in the above mentioned 12 members of this pedigree is of extra ocular origin according to the following arguments (Fig 1 and Fig 4)

- 1 The nystagmus in the subjects IV 15 V 15 V 37 and VI 7 can certainly not be due to defective vision as they all have normal vision
- 2 The spontaneous nystagmus with closed eyes in the subjects IV 15 V 5 V 6 VI 14 VI 16 and VI 35 and the latent nystagmus in total darkness in the subjects V 6 VI 7 VI 14 VI 16 and VI 35 is independent of retinal stimuli
- 3 The examination with the Thorner ophthalmoscope showed in three cases (IV 15 VI 7 and VI 35) a rotating nystagmus which cannot be explained by anomalies of fixation reflexes because a visual reflex rotation of the eyes in a stationary environment does not exist
- 4 Last but not least in an experimental study of latent nystagmus (van Vliet 1978) one of us could prove that latent nystagmus can be independent of retinal stimuli: this argues against an ocular origin of latent nystagmus the established diagnosis of the nystagmus in nine members of the family with Aland eye disease

It must be stressed that repeated examination of this family during a 6 year period has revealed inconsistent findings. It is enough to recall case V 36 and V 38 which illustrated the most extreme that one can meet in this respect. V 36 1963 symmetrical gaze direction nystagmus and spontaneous nystagmus to the left with closed eyes

1969 no nystagmus with both eyes closed open straight ahead or in gaze direction nor when either eye is covered in light or dark nor with ophthalmoscopy or during monocular optokinetic stimulation

V 38 1963 some jerks to the left with closed eyes no nystagmus when either eye is covered

1966 suspect movements of the eyes with ophthalmoscopy

1969 latent nystagmus with ophthalmoscopy

These inconsistencies are common in mild cases of latent nystagmus because the extent to which latent nystagmus occurs depends on

- 1 the difference in monocular gaze intention (van Vliet 1973) and
- 2 age latent nystagmus appears to diminish with age in some patients in as much as the amplitude decreases while the frequency increases until the nystagmus can no longer be detected

In order to understand clearly the relationship between latent nystagmus and the Åland eye disease we have to study all the ocular abnormalities with which latent nystagmus occurs

Concomitant strabismus and alternating hyperphoria are extremely frequent oculomotor symptoms occurring with latent nystagmus. In the Åland family strabismus is mentioned only twice (the pedigree numbers VI 18 and VI 35).

Amblyopia (visual acuity not exceeding 0.5) and refraction anomalies of at least 3 D are encountered in about half the unselected cases of latent nystagmus. In this respect there is little difference in the latent nystagmus of Åland eye disease. Sometimes latent nystagmus is accompanied by other congenital ocular abnormalities such as achromatopsia, cataract, aniridia, albinism and hemeralopia (Kornhuber 1960, van Vliet 1966).

Very little is known about the mode of inheritance of latent nystagmus. According to Dichgans & Kornhuber (1964) latent nystagmus is certainly not X-chromosomal but it is presumably autosomal recessive or irregularly dominant. The studies of 150 cases of latent nystagmus by one of us (van Vliet 1966) would seem to point to a recessive autosomal inheritance though dominant heredity could not be excluded.

As far as we could ascertain in this family from the Åland Islands there was no instance of transmission of latent nystagmus from father to son. This is evidence for the X-chromosomal character of the latent nystagmus in this pedigree.

Owing to the occurrence of gross latent nystagmus in male subjects only and slight latent nystagmus in only two at most three (V 36) female subjects we may assume two possible modes of inheritance of latent nystagmus:

1. an X-chromosomal dominant type of transmission with decreased or lack of penetrance in a number of female carriers
2. a recessive X-chromosomal transmission with slight nystagmus as a sign of heterozygosity in the female carriers

The actual mode of inheritance can be determined only by investigating further offspring.

So far as is known this is the first reported instance with X-chromosomal latent nystagmus. The combination of latent nystagmus with the X-chromosomal Åland eye disease may be explained by pleiotropic gene action.

The remoteness of the phenotype from the primary action of the gene (damage of the embryonic optic cup?) may give rise to a variety of phenotypic effects.

Discussion

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OXYPHENBUTAZONE EYE OINTMENT IN THE TREATMENT OF FOREIGN BODIES IN THE CORNEA

BY

KJELL DYSTER-AAS

In a double blind study 10% oxyphenbutazone (Tanderil®) eye ointment was compared with bibrocathol eye ointment in the treatment of superficial foreign bodies in the cornea of 100 patients. Pain and redness were more quickly alleviated with oxyphenbutazone whereas there was no difference in the effects of the two kinds of treatment on corneal edema and corneal erosion. No ill effects or complications were noted.

Key words: oxyphenbutazone (Tanderil®) - eye ointment - double blind - corneal foreign bodies

Oxyphenbutazone is the active substance of Tanderil®. This anti-inflammatory agent has been used during the past 10 years not only in rheumatic diseases, post-traumatic inflammations and surgery but also in various ophthalmological indications, e.g. scleritis and episcleritis (Watson et al. 1966) and inflammations after cataract, strabismus and glaucoma operations (Nemetz 1972; Younessian & Psilas 1970; Zenklusen 1972).

As there was no controlled comparative clinical trial on oxyphenbutazone eye ointment in the treatment of foreign bodies in the cornea, a double blind study was undertaken in which 10% oxyphenbutazone is compared with a well known eye ointment containing bismuth (bibrocathol). During the course of this study it has been shown in a separate double blind study also on corneal foreign bodies that oxyphenbutazone eye ointment is statistically significantly superior to the plain ointment base (Valk 1972).

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these 11 patients were completely free of symptoms within a few days i.e. they had neither pain redness nor any visual disturbance it seems reasonable to assume they were also free of corneal erosions and edema.

For the statistical analysis the results were examined both with and without the inclusion of these 11 patients. However the results shown in the tables and figures are those after exclusion of these patients.

Pain (Table I Fig 1) Before treatment all patients had at least some pain. Most OPB patients (36) but only half the number of BC patients (9) were free of pain within 1 day of treatment. The difference between the two groups is significant ($P < 0.01$). Within 5 days all patients were without pain.

Table I

Number of patients in the BC and the OPB group arranged according to the four registered parameters: pain, redness, corneal erosion and corneal edema.

Parameter	Degree of symptom	Before treatment		After treatment			
		Day 0		Day 1		Day 2	
		BC	OPB	BC	OPB	BC	OPB
Pain	0	0	0	20	36	9	42
	1	10	8	16	8	9	8
	2	27	36	5	1	4	0
	3	3	1	1	0	0	0

Parameter	Degree of symptom	Before treatment		After treatment	
		Day zero		First control	
		BC	OPB	BC	OPB
Redness	0	0	0	23	39
	1	10	5	10	5
	2	31	36	7	1
	3	1	4	0	0
Edema	0	21	19	25	32
	1	13	18	11	11
	2	8	7	6	2
	3	0	1	0	0
Erosion	0	0	0	37	44
	1	11	11	5	1
	2	23	32	0	0
	3	3	0	0	0

Material and Methods

One hundred consecutive patients with small mostly metallic foreign bodies firmly lodged in the cornea have been treated. After a routine examination the foreign body was removed. All treated corneas were abraded in order to remove as much as possible of the rust ring. The following parameters were recorded:

- 1 Pain
- 2 Redness
- 3 Corneal edema
- 4 Corneal erosions

The same examiner subjectively estimated the symptoms and graded their severity numerically from zero to three. In addition at the control visit a global assessment was made of the result.

Ointments

The patients were treated with 10 % oxyphenbutazone (OPB) eye ointment (Tanderil® eye ointment ZYMA Nyon Switzerland) or 5 % dibrocathol (BC) eye ointment. The ointments were supplied in tubes numbered at random from 1 to 100 and equally divided between OPB and BC. As a further precaution the ointment was always distributed by the nurse, the doctor being told only the number of the tube.

The patients were instructed to apply the ointment three times a day. All patients were treated as out patients.

The treated eye was usually padded during the first 2 days of treatment or until the pain had subsided. The patients were always asked to come back for control examination after 2 days, but due to intervening Sundays and holidays in a few cases these controls had to be postponed for up to 5 days.

Statistics

The sealed code was not broken until all patients had finished treatment and evaluation. The results and significance limits have been calculated with the chi squared test.

Results

The material consists of 100 patients, half of whom were treated with OPB eye ointment and the other half with BC eye ointment. In each group one patient failed to report or to show up for the control examination. Thus there remained 49 patients in each group.

A number of patients in the two groups became free of symptoms in 1 to 3 days. They reported this on the telephone but would not come to the clinic for examination. Thus after treatment four patients in the OPB group and seven in the BC group communicated with the Eye Clinic by telephone only. Since

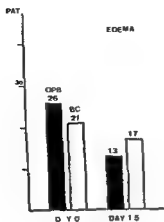


Fig 3

Number of patients having corneal edema before (Day 0) and after (Day 1 - 5) treatment with BC or OPB eye ointment

Edema (Table 1 Fig 3) About half of the patients had corneal edema before treatment. Within 5 days 16 out of 26 OPB patients and 8 out of 21 BC patients were free of edema. The difference is not significant ($P > 0.10$).

Erosion (Table 1 Fig 4) Initially after removing the foreign body an abrasion was performed. Most patients in both groups were healed by the time of their control visit i.e. 44 OPB patients and 37 BC patients. The difference is not significant ($P > 0.10$).

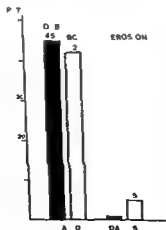


Fig 4

Number of patients having corneal erosions before (Day 0) and after (Day 1 - 5) treatment with BC or OPB eye ointment

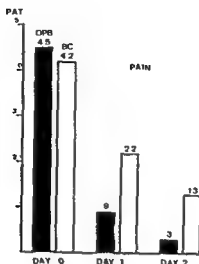


Fig 1

Number of patients reporting pain of the eye before (Day 0) and after (Day 1 and Day 2) treatment with BC or OPB eye ointment

Redness (Table 1 Fig 2) All patients showed initially a conjunctival infection. Within 5 days the redness had disappeared in 39 patients of the OPB group and in 25 of the BC group. The difference is significant ($P < 0.01$).

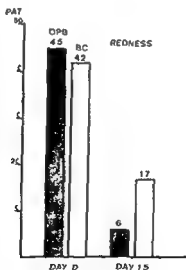


Fig 2

Number of patients showing redness of the eye before (Day 0) and after (Day 1 - 5) treatment with BC or OPB eye ointment

There were no side effects observed after OPB treatment. This is a variance with the study reported by Douglas (1971) on the effect of oxyphenbutazone on glaucomatous eyes. He found punctate stains in the palpebral part of the cornea in a number of treated eyes. No corneal stains were seen in the present study. One reason for this difference might be the duration of the treatment. Douglas treated his patients for 6 weeks whereas in the present study no patient was treated for more than 2 weeks.

The treatment of superficial corneal foreign bodies is rather uniform. The foreign body is removed and the rust ring abraded. Usually some antibiotic or antiseptic eye ointment or eye drops are given and the eye is padded. Fortunately infection rarely is a problem unless secondary infection arises. An anti-inflammatory eye ointment would therefore seem to be a preferable choice. For this and similar indications where the risk of infection is slight and an anti-inflammatory effect is desired, OPB eye ointment may well be used, especially if corticosteroid eye preparations are contra-indicated.

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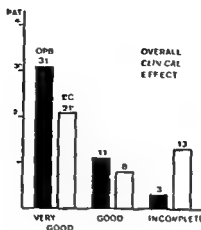


Fig 5

The overall clinical effect from 1 to 5 days after treatment with BC or OPB eye ointment

The treatment had to be changed or supplemented in a few instances in both groups. OPB was replaced twice and BC three times by an antibiotic eye ointment. New abrasion of the cornea had to be performed in four patients in the BC group but in none of the OPB patients. All patients treated only with BC or OPB were told to come back for control examination within 1 week of the last examination if any symptoms persisted. None showed up or telephoned, which can be interpreted to mean that they most likely had healed without complications within this period of time. At the control visit the overall clinical effect of the tested ointments was also noted (Fig 5). Thus in the OPB group there remained three patients with incomplete effect and in the BC group 13 patients. This difference is significant ($P < 0.05$).

The levels of significance obtained if the 11 patients checked by telephone are included are as follows:

Pain $P < 0.025$ redness $P < 0.025$

In the case of edema and erosion the difference remains not significant $P > 0.10$ and for the overall clinical effect the significance is unchanged $P < 0.05$.

DISCUSSION

For the two parameters pain and redness the OPB eye ointment clearly gives a better result than the BC eye ointment and it seems that OPB relieved pain quicker than BC. In the other two parameters edema and erosion the trend is also in favour of OPB but the number of patients is too small to show a statistically significant difference between the two groups.

The imperfection of impression tonometry is caused not only by deficient precision but also by a lack of accuracy** arising from individual variations in factors - other than the intraocular pressure - influencing the resistance offered by the globe to an indentation

Appreciation of this fact once raised expectations that it might be possible to improve the efficiency of Schiøtz tonometry by means of corrections based on measurements of the ocular rigidity

Originally two Schiøtz measurements with different plunger loads on the same eye were used to calculate the coefficient of scleral rigidity which when inserted into Friedenwald's equation (1937) gave a description of the relation hip between pressure and volume in the eye during tonography. This method suffered badly from the lack of precision in Schiøtz tonometry and therefore a Goldmann reading was substituted for one of the two Schiøtz measurements (Schmidt 1936). The combined method however was sensitive to variations in the cushioning effect of the uveal circulation which had the influence on the original method since any major expulsion of blood from the eye during tonometry already occurs with the 5.5 gram plunger load (Ytteborg 1960, Moses & Grodzki 1969). It follows 1) that the combined method cannot be used to estimate the decrease of ocular distension during tonography, 2) that Friedenwald's equation cannot be used to describe the relationship between pressure and volume in the eye during tonometry *in vivo* and 3) that the total ocular rigidity cannot be considered an essentially constant property of the eye.

It may be concluded that measurements of ocular rigidity are of very limited value in practice and that information on individual factors that affect the accuracy of Schiøtz readings should receive increased attention as long as impression tonometers are widely used.

Applanation tonometry is generally considered to be very accurate though not perfectly repeatable. Systematic effects on the relationship between Schiøtz and Goldmann readings can therefore be ascribed to the lack of accuracy in impression tonometry.

Having a material of paired Schiøtz and Goldmann readings derived from a general ophthalmic population survey at our disposal we therefore decided to assess the importance of some factors previously believed to affect the ocular rigidity. To this end we performed a multiple regression analysis with age, sex, refraction and systemic blood pressure together with Schiøtz readings as independent variables and Goldmann readings as the dependent variable.

Precision refers to the ability to give consistent results in repeated trials.
Accuracy refers to the ability to give a true measurement of the item being tested.

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SOME FACTORS AFFECTING THE RELATIONSHIP BETWEEN SCHIÖTZ AND GOLDMANN READINGS IN A POPULATION

BY

BO BENGTSSON

Factors thought to affect the accuracy of Schiötz readings (age sex refraction and systemic blood pressure) were studied by means of a multiple regression analysis in a material of paired Schiötz and Goldmann readings derived from a general ophthalmic population survey. Age was found to be the most important source of variation in the relationship between applanation and impression tonometer readings. The change with age was confined to a relatively short period - from the late fifties to the late sixties. The direction, amplitude and timing of the age effect are such that one important sign of early glaucoma - a rapid rise in ocular tension - may well pass unnoticed by impression tonometry. We conclude that the advisability of Schiötz tonometry for any kind of follow up studies on persons in their sixties should be doubted.

Key words: population study - multiple regression - tonometry Schiötz and applanation - ocular rigidity - age effect - glaucoma

In an earlier report (Bengtsson 1972 b) it was stated that Schiötz tonometry, even when supplemented by Goldmann tonometry, fails to detect persons with moderately increased intraocular pressures to such an extent that its usefulness for routine tonometry and glaucoma screening should be seriously doubted.

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Material

A general ophthalmic population survey was carried out at the Dalby Health Center in southern Sweden from March 1969 to April 1970. Invitations were mailed in rotation following a directory to all persons aged 8 years or more who had been resident in the village surrounding the Health Center since December 1968. Out of 1917 persons invited 1709 (88.8%) took part in the study.

Information about persons who failed to appear or were not examined by both Schiotz and Goldmann tonometry has been given in earlier reports (Bengtsson 1972a,b). Reliable paired readings were obtained in 5106 eyes (1,561 cases). Schiotz readings exceeding 90 were not recorded separately however and therefore 735 eyes with indeterminate Schiotz pressures could not be used for the present purpose. Eleven patients refused to be rendered cycloplegic. Refraction was impossible in one eye of 15 additional cases. Systemic blood pressure was missing in three cases.

Complete information was obtained in 1206 cases (2323 eyes). Their age distribution is given in Table I. Only one eye (the left) from each case was used for determination of the statistical significance of various effects but otherwise both eyes have been included in order to make simple statements equally applicable to right and left eyes.

Methods

Visual acuity ophthalmometry slit lamp examination Goldmann tonometry Schiotz tonometry sphygmomanometric measurements of the systemic blood pressure ophthalmoscopy in mydriasis subjective refraction in cycloplegia and fundus photography were all attempted in every case. Conventional equipment was used according to a fixed program.

Table I
Number of individuals and eyes examined in different age groups

Age (years)	Individuals	Eyes
8 - 9	56	109
10 - 19	901	933
20 - 29	207	369
30 - 39	231	431
40 - 49	188	347
50 - 59	149	277
60 - 69	137	243
70 - 79	78	134
80 - 89	17	31
90 - 99	9	4
Total	1755	2378

Schiotz Goldmann disparities are usually described as the difference between the applanation reading and the pressure given as the equivalent of the Schiotz reading by Friedenwald's 1955 calibration scale. The opinion that such differential values indicate deviations from the intraocular pressure of normal rigidity (Schmidt 1957) should however be modified. Regression curves describing the results of comparisons between Schiotz and Goldmann tonometry deviate greatly from the 1955 calibration scale. The average intraocular pressure in eyes with a given Schiotz reading shows a strong tendency towards the mean, i.e. the applanation pressures tend to be lower than predicted by the calibration scale in eyes with comparatively high Schiotz pressures and vice versa. Such aberrations so called regression effects are an inevitable consequence of all kinds of disagreement between the two methods. Random errors caused by deficient precision are therefore misinterpreted as a lack of accuracy in cases with Schiotz readings above or below the mean if the differential value is accepted as a measure for the rigidity of the eyeball. These deviations cannot be expected to neutralize each other in a truncated material. Since Schiotz readings above 100 are un dependable (Moses & Hahn 1958) the use of differential values therefore seems to imply unavoidable and incalculable errors.

Lately regression equations have been used to convert Schiotz readings into units comparable with Goldmann readings (Anderson & Grant 1970). The differences between the observed applanation pressure and the pressure expected from the Schiotz reading by the regression equation — the residuals — bear a certain resemblance to the differential values of Schmidt. They are however only indirectly related to ocular rigidity and of course not dependent on assumptions concerning the relevancy of calibration scales etc. The residuals are not influenced by the use of one of the independent variables to select the material. We therefore considered them well suited to describe Schiotz Goldmann disparities for our purpose, that of assessing the importance of factors believed to affect the accuracy of Schiotz readings.

The ocular resistance to an indentation can confidently be expected to vary with the size of the globe, the distensibility of the corneo scleral envelope and the cushioning effect of the uveal circulation. Direct measurements of those factors are however not practicable and we must resort to variables such as *refraction* (as an estimate of ocular size), *age and sex* (alleged to be associated with scleral elasticity) and *systemic blood pressure* (probably affecting the amount of choroidal blood available for expulsion during impression tonometry). Some of these variables, e.g. age and blood pressure are strongly correlated. In order to be able to assess the relative significance of the various factors it was therefore necessary to perform a multiple regression analysis.

The main difference between the present procedure and that used in a previous paper to assess factors affecting applanation pressures (Bengtsson 1972) is that Schiotz readings have been introduced (as one of the independent variables). Schiotz readings are after all much more strongly correlated to applanation pressures than any of the tested variables. As soon as Schiotz readings have been added to the regression equation the partial correlations and regression coefficients of the variables tested reflect influences on the relationship between Schiotz and Goldmann readings rather than on applanation pressure itself.

Table II

Multiple regress on analysis of effects of age, blood pressure, tonometer side and sex on the relationship between Schiøtz and Goldmann readings in 238 eyes

Independent variables†				Last step				
				First step	Blood pressure deleted		Blood pressure not deleted	
Denominations	Mean \pm std dev	Total corr coeff	Partial corr coeff		Regr coeff	Std error of regr coeff	Regr coeff	Std error of regr coeff
Schiøtz readings	8.0 ± 0.9 scale div	-0.61	-	-	-0.11550	0.00300	-0.11349	0.00297
Transgenerated age (11)	1.9 ± 4.0 years	0.30	0.37	0.37	0.01270	0.00068	0.00950	0.00080
Refract in	0.6 ± 1.5 diopters	-0.01	-0.05	-0.05	-0.01100	0.00700	-0.01900	0.00700
Systolic blood pressure	132 ± 12 mmHg	0.31	0.27	0.27	-	-	0.00090	0.00014
Tonometer	1.5 ± 0.5	0.12	0.00	0.00	0.07321	0.00540	0.07846	0.00541
Side	1.5 ± 0.5 *	-0.02	-0.10	-0.10	-0.07469	0.00516	-0.07447	0.00511
Sex	1.5 ± 0.5 *	0.10	0.07	0.07	0.01597	0.00517	0.01504	0.00511
Age (not transgenerated)	38 ± 10 years	0.95	0.96	0.96	(not entered)	(not entered)	(not entered)	(not entered)
Diastolic blood pressure	94 ± 11 mmHg	0.25	0.23	0.23	(not entered)	(not entered)	(not entered)	(not entered)
Y axis intercept				3.63	3.58	3.44	3.44	3.44
Mean square of residual				0.01760	0.01590 (-1.3%)	0.01502 (-1.5%)	0.01502 (-1.5%)	0.01502 (-1.5%)
Std error of estimate				0.153	0.124 (-7%)	0.129 (-8%)	0.129 (-8%)	0.129 (-8%)
Multiple corr coeff				0.612	0.677	0.635	0.635	0.635

* Winter = 1 Summer = 0

† Right = 1 Left = 0

* Male = 1 Female = 0

† Dependent variable in Goldmann readings (2.7 ± 0.17)

The *applanation tonometry* was performed by one ophthalmologist using a Goldmann tonometer mounted on a Haag Streit 900 slit lamp. The tonometer was tested at PTB in Berlin and found to be completely devoid of demonstrable errors in the pertinent pressure range (For method see Jessen 1969). The right eye was always measured first; the instrument was read to the nearest millimeter and the first reliable reading was recorded.

The *impression tonometry* was performed by one nurse using two Schiøtz tonometers. The first tonometer (manufactured and certified by SKLAR) was used up until November 1969 – when it was replaced by a second tonometer (manufactured by Winter) which had been tested and approved by PTB in Berlin (For method see Jessen 1969). The SKLAR tonometer was later tested at the tonometer station in Uppsala and found to be fit for routine use.

In order to get a continuous variable the same tonometer weight had to be used in all cases. The 7.5 g plunger load was chosen since it was expected to afford the most useful pressure range considering that only readings between 30 and 100 were to be used (Moses & Hahn 1958; Friedenwald 1954). In fact no readings smaller than 30 were encountered and for technical reasons readings exceeding 90 were not recorded separately.

The right eye was measured before the left. The first successful application of the tonometer in each eye was used. The nurse had been instructed to read the tonometer to the nearest half of a scale division.

The systolic and diastolic blood pressures were measured on the right arm, the patient remaining in a recumbent position after Schiøtz tonometry, by a nurse using a mercury manometer read to the nearest 5 mmHg, inflatable arm cuffs of appropriate sizes and a stethoscope.

All data were immediately codified and recorded on special forms. Transfer to punch cards and further processing were performed at the Computer Center in Lund. The regression analysis was carried out with two standard computer programmes – BMD 02R and BMD 03R (Dixon 1970).

The goal of the regression analysis was to derive an equation expressing Goldmann readings as a mathematical function of Schiøtz readings taking possible sources of variation into consideration by including them as additional independent variables.

The regression equation has the form $y = a + b_1x_1 + \dots + b_qx_q + e$ where y is the dependent variable, a a constant called the y intercept, x_1, \dots, x_q independent variables, b_1, \dots, b_q constants called regression coefficients and e an error term called the residual. Non linear equations can easily be obtained since the computer programmes allow transgenerations of simple variables.

Friedenwald's 1955 calibration scale forms a nearly straight line in a semilogarithmic plot and Anderson & Grant (1970) have recently shown that a semilogarithmic form of the regression equation is likely to give the closest fit. Moreover plots of frequency distributions on probability paper of the logarithm of applanation readings in eyes with identical Schiøtz readings were linear in our material allowing us to expect the residuals after the initial step to be approximately normally distributed – an advantage though not a prerequisite in this type of analysis. Therefore the Goldmann readings were transgenerated into their (natural) logarithms prior to their insertion into the regression equation.

Table II

Multiple regression analysis
Effects of age blood pressure tonometer side and sex on the relationship between Schiotz and Goldmann readings in 509 yrs

Independent variables†				First step		Last step			
Denominators	Mean \pm std dev	Total corr coeff	1st partial corr coeff	Blood pressure deleted		Blood pressure not deleted		1st partial corr coeff	
				Regr coeff	Std error of regr coeff	Regr coeff	Std error of regr coeff		
Schiotz readings	90 ± 0.9 scaled div	-0.61	-	-0.11550	0.00900	-0.11542	0.00207	-	-
Transgenerated age (P_{11})	19 ± 4.0 years	0.30	0.37	0.01970	0.00068	0.00950	0.00080	-	-
Refraction	0.6 ± 1.5 diopters	-0.01	-0.05	-0.01100	0.00200	-0.01200	0.00700	-	-
Systolic blood pressure	152 ± 7.7 mmHg	0.31	0.97	-	-	0.00090	0.00014	-	-
Tonometer	1.5 ± 0.5 *	-0.12	0.00	0.07391	0.00540	0.07346	0.00541	-	-
Side	1.5 ± 0.5	-0.07	-0.10	-0.07469	0.00516	-0.02447	0.00511	-	-
Sex*	1.5 ± 0.5 *	0.10	0.07	0.01577	0.00517	0.01504	0.00511	-	-
Age (not transgenerated)	39 ± 7.0 years	0.75	0.96	(not entered)	(not entered)	(not entered)	(not entered)	0.01	0.01
Diastolic blood pressure	94 ± 11 mmHg	0.75	0.93	(not entered)	(not entered)	(not entered)	(not entered)	0.02	0.02

Y axis intercept

3.63

3.53

3.44

Winter = 1 Summer = 2

0.01760

0.01530 (-1.5%)

0.01502 (-1.5%)

Right = 1 Left = 2

0.133

0.174 (-7%)

0.107 (-8%)

** Male = 1 Female = 2

0.612

0.685

† Dependent variable in Goldmann readings (27 ± 0.17)

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The regression equation has the form $y = a + b_1x_1 + \dots + b_kx_k + e$ where y is the dependent variable, a a constant called the y intercept, x_1, \dots, x_k independent variables, b_1, \dots, b_k constants called regression coefficients and e an error term called the residual. Non-linear equations can easily be obtained since the computer programmes allow transgenerations of simple variables.

Friedenwald's 1955 calibration scale forms a nearly straight line in a semilogarithmic plot and Anderson & Crisp (1970) have recently shown that a semilogarithmic form of the regression equation is likely to give the closest fit. Moreover plots of frequency distributions on probability paper of the logarithm of applanation readings in eyes with identical Schiøtz readings were linear in our material, allowing us to expect the residuals after the initial step to be approximately normally distributed – an advantage though not a prerequisite in this type of analysis. Therefore the Goldmann readings were transgenerated into their (natural) logarithms prior to their insertion into the regression equation.

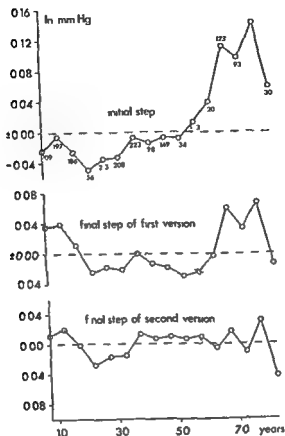


Fig 2

Change in mean residual with age (continuous line) and age correction (dotted line) after indicated steps and versions of the multiple regression analysis. The numbers represent the number of observations in each class. The careful reader may notice that the mean residual is also affected by the other variables in the regression equation (e.g. blood pressure).

Each transgeneration of age was then tested separately for its ability to reduce the residual variance when replacing age in the multiple regression equation. Variable P_{11} ($a = 56$, $b = 68$) was the most effective in this respect, closely followed by P_8 ($a = 54$, $b = 69$) and P_{13} ($a = 57$, $b = 67$). In fact, any one of the thirteen modifications of 1 tested had considerably more effect on the relationship between Schiøtz and Goldmann readings than any of the original variables.

On these grounds we tentatively allowed variable P_{11} to replace age in a

Results

To start with we tested age sex refraction systolic blood pressure diastolic blood pressure side and tonometer in addition to Schiötz readings as independent variables

A standard programme (BMD 02R) was used to compute a sequence of multiple linear regression equations in a stepwise manner. At each step the variable which had the highest partial correlation with the (natural) logarithm of Goldmann readings was added to the regression equation. As expected Schiötz readings were entered first. The partial correlation of diastolic blood pressure was practically abolished as soon as the systolic blood pressure was added to the regression equation but otherwise all the variables tested had definite independent effects on the relationship between Schiötz and Goldmann readings.

A number of multiple regression analyses (BMD 03R) within subsamples of the population – intended to reveal interactions between the different variables – disclosed however that the effect of age was confined to persons more than 40 years old. Plots of the residuals versus input variables – provided by the standard programme (BMD 02R) – confirmed that the age effect was non linear and indicated a rapid change in the relationship between Schiötz and Goldmann readings from the late fifties to the late sixties. The effects of systolic blood pressure and refraction on the other hand seemed to be approximately linear.

We therefore constructed an assortment of transgenerations of age to be called P_{1-13} according to the following specifications

$$P = 0 \text{ if age} \leq a$$

$$P = \text{age} - a \text{ if } a \leq \text{age} \leq b$$

$$\text{and } P = b - a \text{ if age} \geq b$$

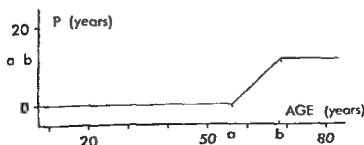


Fig. 1
Transgeneration of age

where a and b were given values from 54 to 60 and from 64 to 70 respectively

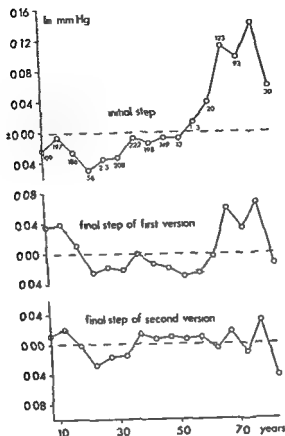


Fig 2

Change in mean residual with age (continuous line) and age correction (dotted line) after indicated steps and versions of the multiple regression analysis. The numbers represent the number of observations in each class. The careful reader may notice that the mean residual is also affected by the other variables in the regression equation (e.g. blood pressure).

Each transgeneration of age was then tested separately for its ability to reduce the residual variance when replacing age in the multiple regression equation. Variable P_{11} ($a = 56$ $b = 68$) was the most effective in this respect, closely followed by P_8 ($a = 54$ $b = 69$) and P_{13} ($a = 57$ $b = 67$). In fact, any one of the thirteen modifications of P tested had considerably more effect on the relationship between Schiotz and Goldmann readings than any of the original variables.

On these grounds we tentatively allowed variable P_{11} to replace age in a

modified multiple regression equation (Table II) The effects of the other variables remained largely unaltered but the partial correlation of age (not transgenereted) with the (natural) logarithm of Goldmann readings was virtually abolished (Table II) and plots of the mean residual against age in the whole material (Fig 2) demonstrated the efficiency of variable P_{11} in accounting for the changes in the relationship between Schiötz and Goldmann readings with age Similar plots in suited subsamples of the population showed that the selected transgeneration of age was equally effective in both sexes (Fig 3) and independent of Schiötz readings (Fig 4)

Keeping to left eyes – in order not to use data invalidated by duplication due to similarities between the two eyes of an individual (cf Anderson & Grant 1970) – we assessed the statistical significances of the regression coefficients from T values computed by the standard programme (BMD 03R) The effect of sex was found to be probably significant ($0.05 > P > 0.01$) the effects of refraction systolic blood pressure and tonometer highly significant ($P < 0.001$) and that of transgenerated age (variable P_{11}) most significant The effect of side seemed comparable to that of tonometer (Table II)

Available data therefore indicated that the second version of the multiple regression equation – given in Table II and expressing the (natural) logarithm of Goldmann readings as a linear function of Schiötz readings a transgeneration of age called P_{11} refraction systolic blood pressure tonometer side and sex – provided the best description of our observations concerning the sources of variation in the relationship between Schiötz and Goldmann readings

In practice however information about blood pressure is often lacking In that case the fact that the blood pressure rises with age should be taken into consideration To this end the results of a multiple regression analysis in which blood pressure was deleted were included in Table II

Discussion

The relationship between Schiötz and Goldmann readings was noticeably affected by age refraction blood pressure tonometer and side in our material The effect of sex on the other hand was negligible though probably statistically significant

The total reduction in "mean square of residual" from the first step (in which only Schiötz readings were added to the regression equation) to the last was 15% (Table II) In view of the fact that we had to resort to variables (age refraction and blood pressure) that could be expected to have only indirect effects on the ocular resistance to an indentation this figure amply confirms the lack of accuracy in impression tonometry

A given Schiøtz reading corresponded to a lower Goldmann reading in left than in right eyes. The reason for this was that while our Goldmann readings were unaffected by side the average Schiøtz reading was lower in left eyes. Presumably the application of the Schiøtz tonometer was more difficult to manage on the left than on the right eye – the patient's nose being a hindrance to the right handed observer.

Readings obtained by impression tonometry are adversely influenced by unavoidable mechanical disparities between individual tonometers. The difference between our two tonometers was limited to one quarter of a scale division. This finding is however by no means incompatible with the opinion that the range of such disparities is too wide to permit uniformity in the clinical experience derived from different though certified tonometers (Armaly 1960, Anderson & Grant 1960).

In our material the effect of different levels of blood pressure on the relationship between Schiøtz and Goldmann readings can for the most part be explained as a regression effect caused by the fact that the intraocular pressure is higher in persons with high blood pressure (Bengtsson 1972a, b). The cushioning effect of the uveal circulation may nevertheless be of considerable importance of course as reported by Ytteborg (1960), Comberg & Pilz (1961) and Moses & Grodzka (1969).

The resistance offered by the eyeball to a change in intraocular volume is dependent on the size of the globe which to a great extent also determines the refraction. In practice Schiøtz readings on myopic eyes are viewed with suspicion. No conclusions regarding high myopes can be drawn from our data which nevertheless support the opinion that a restriction of precautionary measures to myopes is unwarranted.

In a previous paper (Bengtsson 1972a) the over all rise in ocular tension with age was shown to be dependent on a concomitant rise in systemic blood pressure. The effect of blood pressure as well as that of age on the intraocular pressure is however less impressive with the Schiøtz tonometer than with the Goldmann tonometer. Since previous studies of the influence of age on ocular rigidity have given inconsistent results (Friedenwald 1937, Draeger 1959, Drance 1960, Mehra 1963) we felt compelled to state that a discrepancy between the two methods could be explained assuming that not only the ocular tension but also the amount of choroidal blood available for expulsion by the tonometer is affected by the systemic blood pressure.

Therefore it greatly surprised us to find that age was by far the most important source of variation in the relationship between Schiøtz and Goldmann readings in our material. The importance of this factor is further emphasized by our equally astonishing findings that the change with age was confined

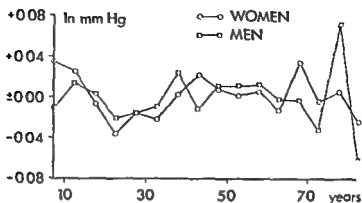


Fig 3

Change in mean residual with age in subsamples of the population

to a relatively short period from the late fifties to the late sixties. Taking variations in ageing into consideration such an effect of age in the population seems to imply a still faster change in the relationship between Schiötz and Goldmann readings in the individual. In this context it should be recalled that Strömberg (1962) concluded that the more severe forms of ocular hypertension in otherwise normal eyes usually develop rapidly during the years between 60 and 70. The speculation that a change in the wall of the eye which is supposed to cause the increase in ocular tension may also cause a decrease in the resistance offered by the globe to an indentation is unavoidable. The direction, amplitude and timing of the age effect according to our observations are such that one important sign of early glaucoma – a rapid rise in ocular tension (Armaly 1969) – may well pass unnoticed by impression tonometry.

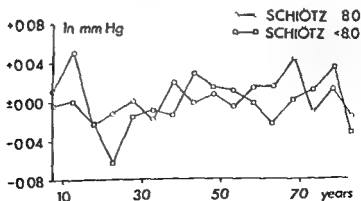


Fig 4

Change in mean residual with age in subsamples of the population

We must conclude that our doubts about the usefulness of Schiøtz tonometry for glaucoma case detection should be supplemented by similar doubts about the advisability of impression tonometry for any kind of follow-up studies on persons in their sixties

Acknowledgments

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TOPICAL CORTICOSTEROIDS AND VITREOUS DYNAMICS IN THE RABBIT

BY

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NANDO PELLEGRINO

The instillation of 0.2% 9 α fluoro 16 α methylprednisolone twice daily in the left eye of rabbits for 30 days induced significant biochemical changes in the vitreous body. Actually a marked acidification accompanied by a decrease in the buffer base, a notable increase in osmotic pressure and a reduction in the ascorbic acid content were observed. These changes are compared with those evidenced in the blood and aqueous humor. An interpretation of the data obtained is suggested on the basis also of the close relationship existing between the vitreous and the retina.

Key words: vitreous - ascorbic acid - acid base status - osmotic pressure - corticosteroids - rabbit

A condition of blood acidosis was shown to be accompanied by and to proceed in parallel with an acidosis of the aqueous humor and a decrease in the intraocular pressure (Vino et al 1970 a b c 1971 Bietti et al 1971 1972 a b).

On this presupposition it is actually based the use of blood acidifying agents in treating various conditions involving intraocular hypertension.

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Even though it has not been possible to prove that a condition of alkalosis of both blood and aqueous humor is related to an intraocular hypertension we think that our previous experimental works (Virno et al 1971, Bietti et al 1972 a, b) have proven that an alkalosis and an increase in intraocular tension often are associated. The instillation of corticosteroids the ocular hypertensive effects of which were described in 1954 by François was accompanied in all our experiments by an alkalosis of the aqueous humor and by a gradual and marked reduction in the aqueous humor ascorbic acid content and frequently also by an increase in ocular tension.

In consideration of such results we deem that even if a close parallelism between alkalosis and ocular hypertension is not always observed at least in the case of corticosteroid instillation one of the more characteristic biochemical changes in the aqueous humor induced by these drugs is a shift towards alkaline values of the acid base status and a marked decrease in the ascorbic acid content.

We therefore decided to investigate the vitreous dynamic. The aim of the present research was to study possible physico chemical changes which might be effected in the vitreous body by prolonged corticosteroid instillation which is the most common way to administer these agents in treating various ocular pathological conditions. At the same time the blood and aqueous humor acid base status and the ascorbic acid content of aqueous and lens were examined.

Methods

Sixteen pigmented rabbits weighing approximately 3 kg and maintained at a constant food and water intake were given 0.2% 9 α -fluoro-16 α -methylprednisolone (Luxizone Tubi Lux, Pomezio, Italy) in the left eye twice daily for 30 days. The right eye was used as a control.

Before and at intervals of 10, 20 (blood and aqueous) and 30 days (blood, aqueous, vitreous and lens) after treatment the following determinations were made:

- intraocular pressure
- pH and alkali reserve (standard bicarbonate and base excess) of blood, aqueous and vitreous
- ascorbic acid content of aqueous, vitreous and lens
- osmotic pressure of vitreous
- glutathione levels of lens

Blood was taken from the ear marginal vein. Aqueous humor was collected following topical anesthesia with Novesine Winder 0.4%.

For vitreous and lens determinations the eyes were enucleated following general anesthesia (Nembutal sodium 30 mg/kg body weight intravenously) and immediately frozen at -10°C for 12 hours. Subsequently the sclera was incised radially and vitreous and lens were carefully dissected free and allowed to melt for 1 hour at room temperature. The vitreous was then filtered through a wide mesh gauze.

Intraocular pressure was measured with the Mackay Marg electronic tonometer. pH and alkali reserve were determined by the Radiometer Micro Astrup apparatus. Osmotic pressure was evaluated with the Fiske osmometer. Ascorbic acid content was measured by the colorimetric method of Sullivan & Clarke (1935) modified by Bonomi (1964). Lens glutathione was determined by the colorimetric method of Fujita & Numata (1938).

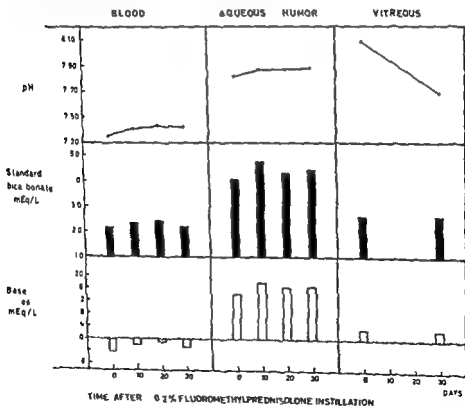


Fig 1

Comparative data on the acid base status of blood, aqueous humor and vitreous before and at different time intervals after instillation of 0.2% 9α-fluoro 16α-methylprednisolone twice daily in the left eye of rabbits (mean values from 16 rabbits)

Even though it has not been possible to prove that a condition of alkalosis of both blood and aqueous humor is related to an intraocular hypertension we think that our previous experimental works (Virno et al 1971, Bielli et al 1972 a, b) have proven that an alkalosis and an increase in intraocular tension often are associated. The instillation of corticosteroids the ocular hypertensive effects of which were described in 1954 by François was accompanied in all our experiments by an alkalosis of the aqueous humor and by a gradual and marked reduction in the aqueous humor ascorbic acid content and frequently also by an increase in ocular tension.

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0.2% FLUOROMETHYLPREDNISOLONE INSTILLATION TWICE DAILY IN THE RABBIT

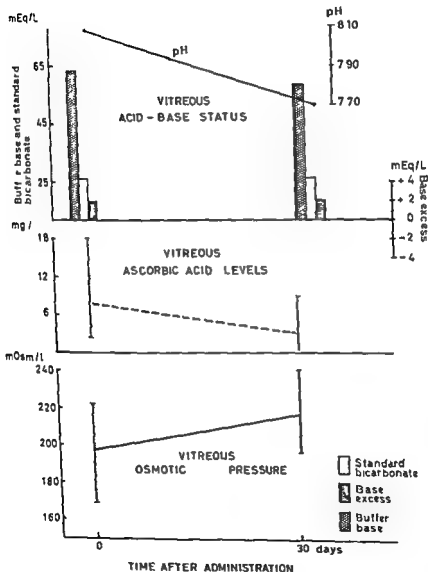


Fig 2

Behavior of acid base status of ascorbic acid content and of osmotic pressure of the vitreous body before and after 30 days of instillation of 0.2% 9 α fluoro 16 α methyl prednisolone twice daily in the left eye of rabbits (mean values from 16 rabbits)

Table I
Blood and aqueous humor mean acid base status following 0.2% fluoromethylprednisolone instillation in the rabbit

	pH				Standard bicarbonate mEq/l				Base excess mEq/l			
	Time after treatment (days)				Time after treatment (days)				Time after treatment (days)			
	0	10	20	30	0	10	20	30	0	10	20	30
Blood mean values	7.36	7.41	7.43	7.42	21.7	22.9	23.4	22.1	-3.80	-2.12	-1.43	-2.86
Aqueous humor mean values	7.82	7.81	7.87	7.93	40.6	47.6	43.4	44.1	+14.5	+18.1	+16.2	+16.7

Table II
Mean acid base status osmotic pressure and ascorbic acid levels of the vitreous following 0.2% fluoromethylprednisolone instillation in the rabbit

	pH		Standard bicarbonate mEq/l		Base excess mEq/l		Buffer base mEq/l		Osmotic pressure mOsm/l		Ascorbic acid mg %	
	Test	30 days	Test	30 days	Test	30 days	Test	30 days	Test	30 days	Test	30 days
Mean values	8.09	7.60	26.5	26.7	+3.2	+3.0	64	58	198	217	8.0	3.0

Results

The treatment by means of 9 α fluoro 16 α methylprednisolone twice daily for 30 days in the left eye of rabbits induced in the aqueous humor a marked shift of the pH towards the alkaline values (mean increase of 0.19 pH unities) and an increase in the alkali reserve (mean increase of 1.35 mEq/l and of 2.06 mEq/l respectively for the standard bicarbonate and for the base excess). Blood behaved in a similar manner yet the changes were less significant (Fig 1 and Table I).

The pH of the vitreous showed a marked shift towards acid values the average decrease was 0.39 pH unities. The base excess and standard bicarbonate showed no changes whereas the buffer base was reduced. The osmotic pressure proved to be increased (mean value 21 mOsm/l) (Fig 2 and Table II).

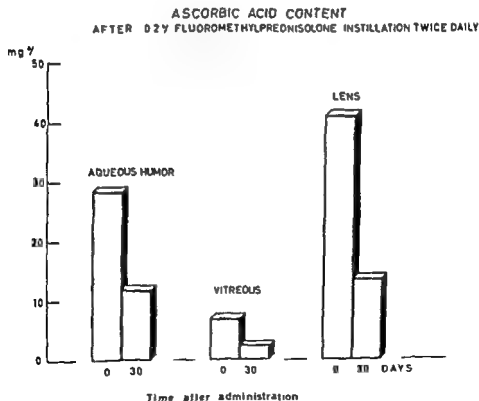


Fig 3

Comparative data on the behavior of the ascorbic acid content of vitreous aqueous humor and lens before and after 30 days of instillation of 0.2% 9 α fluoro 16 α methyl prednisolone twice daily in the left eye of rabbits (mean values from 16 rabbits)

These results seem to us to be particularly interesting in view of the well known importance of the ascorbic acid at the ocular level. As a matter of fact the influence of ascorbic acid on the permeability of the trabecular meshwork is generally recognized because of the close relationship between hyaluronic acid and ascorbic acid: the absence or the decrease of the latter actually increases the amount of hyaluronic acid in the tissues thus compromising their diffusibility (Lieb & Stark 1966; Heath 1962). The increase in the intraocular pressure which in the present research was shown to average 5.5 mmHg finds its explanation in this theory.

As far as the decrease in lens glutathione is concerned we may suppose as follows. As the lens glutathione would participate in the oxido-reduction processes responsible for the reduction of dehydroascorbic acid to ascorbic acid in the lens, a reduced glutathione content could undoubtedly imply a decrease in the ascorbic acid. This has been observed by us. Moreover it was suggested that the lens ascorbic acid was essential for the maintenance of normal levels of this substance in the vitreous and aqueous humor. This could explain why the ascorbic acid is decreased in both areas.

The data actually at our disposal as yet do not allow us to determine on which factor — glutathione or ascorbic acid — the corticosteroids are acting primarily.

The marked acidification of the vitreous body is only apparently in contrast with what we have just said. The close relationship existing between retina and vitreous body makes it possible for the latter to be promptly influenced by the metabolic changes in the retina (Brini et al 1968). Moreover the corticosteroids regulate the glycogen content at the tissue level and influence the glycolytic activities of the tissues (Houssay 1953). Thus the prolonged administration of high dosages of fluoromethylprednisolone which is likely to involve the blood as well could not but produce an increase in the glycolysis at the retinal level with a consequent accumulation of acid catabolites (pyruvic and lactic acid) (Brini et al 1969). It should be mentioned that among all body tissues the retina is actually known to have the highest rate of aerobic and anaerobic glycolysis (Warburg 1956).

The increase in the osmotic pressure of the vitreous might presumably be attributed both to the accumulation of acid catabolites coming from the retina and to the increase in the hyaluronic acid which is no longer depolymerized owing to the well known anti-hyaluronidase action of the corticosteroids (Larsen 1958; Kaplan & Fisher 1964; Battini et al 1964; François 1954, 1961; Liouquet 1970).

The behavior of the buffer base expression of the non-respiratory acid-base status lends support to the interpretation of our results.

Table III

Mean ascorbic acid and glutathione levels of the lens following 0.2% fluoromethyl prednisolone in the rabbit

	Ascorbic acid levels mg %		Glutathione mg %	
	Test	30 days	Test	30 days
Mean values	49	15	449.9	319.9

The ascorbic acid content of the three areas examined (aqueous humor, vitreous and lens) was shown to decrease significantly after 30 days of steroid administration. Mean decreases were respectively 16.50, 4.69 and 30.67 mg % (Fig. 3). Lens glutathione was reduced from 449.9 mg % to 319.9 mg % (Table III).

The intraocular pressure was shown to increase after 30 days of steroid treatment with a mean value of 5.5 mmHg.

Discussion

The administration of 9 α -fluoro-16 α -methylprednisolone induced significant biochemical changes of the three areas examined: vitreous body, aqueous humor and lens.

A slight shift of the acid-base status towards alkaline values moreover was noted in the blood; this might be attributed to the high dosages employed as compared with the weight of the experimental animal. It may be assumed that we thus attained the electrolyte changes which usually accompany the systemic administration of high dosages of corticosteroids.

The aqueous humor parameters underwent all significant variations as an expression of the biochemical disturbance provoked by the prolonged steroid application. The more important data concern the relationship between ascorbic acid content and the acid-base status. In the present research as well as in that previously carried out by us (Virno et al. 1970; a, b, c 1971; Bietti et al. 1972) the fluoromethylprednisolone instillation always induced a decrease in the ascorbic acid content and a concomitant shift towards alkaline values of the acid-base status.

This research moreover evidenced that also the ascorbic acid contents of vitreous and lens were significantly decreased.

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The coexistence of a condition of alkalosis in the anterior chamber and of a condition of acidosis in the vitreous body should not be surprising in consideration both of the scarce diffusibility of the substances in the vitreous and of the bicarbonate gradient occurring between the ciliary body and the anterior chamber on one side and between the ciliary body and the vitreous on the other (Kinsey & Reddy 1959)

It may be concluded that the topical administration of 9 α fluoro 16 α methyl prednisolone induced the following conditions in the rabbit

- an increase in the intraocular pressure
- a slight alkalosis of the blood attributable to the systemic absorption of the drug because of the high dosages used
- a significant alkalosis of the aqueous humor
- a marked decrease in the ascorbic acid content of the aqueous humor lens and vitreous
- a notable shift towards acidity of the pH values of the vitreous accompanied by a decrease in the buffer base which presumably is attributable to an accumulation of acid catabolites as a result of the increased glycolytic activity of the retina effected by the corticosteroids This is further supported by the marked increase in the vitreous osmotic pressure

Further investigations are being undertaken in order to confirm our hypotheses and to establish the significance of our data especially with a view to achieving a better understanding of the pathogenesis of steroid glaucoma and cataract

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The coexistence of a condition of alkalosis in the anterior chamber and of a condition of acidosis in the vitreous body should not be surprising in consideration both of the scarce diffusibility of the substances in the vitreous and of the bicarbonate gradient occurring between the ciliary body and the anterior chamber on one side and between the ciliary body and the vitreous on the other (Kinsey & Reddy 1959)

It may be concluded that the topical administration of 9 α fluoro 16 α methyl prednisolone induced the following conditions in the rabbit

- an increase in the intraocular pressure
- a slight alkalosis of the blood attributable to the systemic absorption of the drug because of the high dosages used
- a significant alkalosis of the aqueous humor
- a marked decrease in the ascorbic acid content of the aqueous humor lens and vitreous
- a notable shift towards acidity of the pH values of the vitreous accompanied by a decrease in the buffer base which presumably is attributable to an accumulation of acid catabolites as a result of the increased glycolytic activity of the retina effected by the corticosteroids. This is further supported by the marked increase in the vitreous osmotic pressure

Further investigations are being undertaken in order to confirm our hypotheses and to establish the significance of our data especially with a view to achieving a better understanding of the pathogenesis of steroid glaucoma and cataract

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The anomaloscope test gives more precise information about the type of colour defects (Pickford 1967 Lakowski 1969) and is equally useful in assessing acquired dyschromatopsia (Verriest 1963 Lakowski 1971 Krill & Fishman 1971) Therefore the present study was undertaken

Material and Methods

Twelve male patients with mean age of 60.7 years in whom the diagnosis of tobacco amblyopia was very definite and 12 normal controls matched for sex and age (mean age 60.9 years) were included in this study. The patients were all pipe smokers with bilateral acquired defect of visual acuity associated with bilateral centrocaecal scotoma and acquired defective colour discrimination of Red Green type. Two tests - Pickford Nicolson Anomaloscope and Farnsworth Munsell 100 Hue test - were employed to diagnose the colour vision defect.

The Pickford Nicolson anomaloscope P N anomaloscope (Pickford 1957 Pickford & Lakowski 1960) is a simple colorimeter employing filtered light which passes through a viewing aperture which subtends an angle of 1.5° at the eye at a distance of 1 metre. The viewing aperture is split vertically into two parts: a standard and a variable, where the standard is the stimulus to be matched by a mixture of two primaries of the variable. The subject is required to match the stimulus on the left side with a mixture of two primary colours on the right side.

In this study the test was carried out binocularly with the subject viewing the aperture at a distance of one metre. Only the Rayleigh equation Red + Green = Yellow was used. Colour discrimination was measured by an assessment of the Matching Range and the Mid matching point in terms of dial scale on the instrument.

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TOBACCO AMBLYOPIA AND ACQUIRED DYSCHRMATOPSIA ANOMALOSCOPE TESTS

BY

S K BHARGAVA

The colour vision of 12 patients with tobacco amblyopia and 12 normal controls matched for age and sex was tested with the Pickford Nicolson anomaloscope and the Farnsworth Munsell 100 Hue test. The results of the two tests were correlated ($r = +0.68$ $P < 0.01$) in that the higher the matching range on the P N anomaloscope the greater is the error score on the 100 Hue test in tobacco amblyopia. The matching range ($t = 9.78$ $P < 0.001$) and the 100 Hue test ($t = 5.43$ $P < 0.001$) score were significantly higher than those of the controls. The acquired colour defect in tobacco amblyopia with the P N anomaloscope is of extreme protanomalous type - the mean mid matching point being shifted towards the red by more than the 3 s.d. limits for the normal controls.

Key words acquired dyschromatopsia - tobacco amblyopia - anomaloscope - matching range - 100 Hue test - error score

Acquired dyschromatopsia in tobacco amblyopia is well documented (Dowling 1908 Carroll 1935 Herbolzheimer 1942 Heaton et al 1955 Silvette et al 1960 François & Verriest 1961 Chisholm et al 1967 Watson Williams et al 1969 Chisholm 1969). The Farnsworth Munsell 100 Hue test (Farnsworth 1943 1957) is an excellent test for acquired colour vision defect (François & Verriest

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1961 Verriest 1963 Lakowski 1968 1969) and it predominantly shows Red Green type of colour defect in tobacco amblyopia on profile (Amley 1970 Chisholm Bronte Stewart & Awduche 1970) and the extent of colour discrimination is represented quantitatively by error score (Chisholm 1969 Foulds et al 1970) As acquired dyschromatopsia is complex and not quite as clear cut as congenital colour defects (Verriest 1963) it is difficult to distinguish on the 100 Hue profile between deutan and protan types of RG colour defects especially when the error score is high because of difficulty in finding a definite axis of confusion (Cox 1960 1961 François & Verriest 1961 Krill & Fishman 1971) Also on the 100 Hue profile there is some overlap of axis of confusion of protan and deutan (Taylor 1968 Linsz 1971)

The anomaloscope test gives more precise information about the type of colour defects (Pickford 1967 Lakowski 1969) and is equally useful in assessing acquired dyschromatopsia (Verriest 1963 Lakowski 1971 Krill & Fishman 1971) Therefore the present study was undertaken

Material and Methods

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The Pickford Nicolson anomaloscope P N anomaloscope (Pickford 1957 Pickford & Lakowski 1960) is a simple colorimeter employing filtered light which passes through a viewing aperture which subtends an angle of 1.5° at the eye at a distance of 1 metre. The viewing aperture is split vertically into two parts a standard and a variable where the standard is the stimulus to be matched by a mixture of two primaries of the variable. The subject is required to match the stimulus on the left side with a mixture of two primary colours on the right side.

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F-M 100-Hue test The colour discrimination and colour confusion were also measured by using the F M 100 Hue test (Farnsworth 1957) and the total error score was calculated. The test was given binocularly on the patients as well as on the normal controls under standard illumination provided by Macbeth Day light lamp BBX 324.

Results

The results of patients on P N anomaloscope and F M 100 Hue tests are presented in Table 1 and are compared with those of the normal controls.

P-N Anomaloscope

The findings on the tobacco amblyopes with the P N anomaloscope differ from those on the normal controls in the following ways.

1 Mid-matching point The mean mid matching point is significantly different from that of the normal controls and is shifted towards the red by paired comparison *t* test ($t = 2.94$ $df = 11$ $P < 0.02$). The shift towards the red was greater than the 3 \times s.d. limit for the normal controls.

2 Matching range The difference in matching ranges of the tobacco amblyopes and the normal controls is also highly significant by paired comparison *t* test ($t = 9.78$ $df = 11$ $P < 0.01$).

F M 100-Hue test

Error score There is a highly significant difference between the error scores of the two groups ($t = 5.43$ $df = 11$ $P < 0.001$) the tobacco amblyopes showing the higher score. The error scores of the normal controls are within the 95th percentile limit for their age (Verriest 1963) while the tobacco amblyopes error scores are well outside that limit.

Profile In eight patients in whom the total error scores were more than 300 the profile was either completely anarchic or although suggesting RG colour defect preferentially the bipolar clustering of the errors were too irregular and widespread to determine the axis of confusion with any accuracy. In the other four patients the profiles resembled that of a deutan.

When the 100 Hue error score was plotted against the mid matching point no correlation ($\rho = 0.16$ $P > 0.05$) was found but a significant correlation ($\rho = +0.768$ $P < 0.01$) was found between the 100 Hue error score and the matching range in that the higher the error score the higher is the matching

Table 1
Data for 1st patients with tobacco amblyopia and 12 normal controls on Pickford-Nicolson Anomaloscope
and Farnsworth Munsell 100 Hue test

Patient no	Age		Visual acuity		Matching range		Mid matching point		100 Hue Score	
	Patient	Control	Patient	Control	Patient	Control	Patient	Control	Patient	Control
1	78	78	5/60	6/6	3°	7	30.0	3° 5	672	170
2	58	58	6/74	6/6	30	4	31.0	30.0	444	28
3	74	74	6/36	6/6	20	8	20.0	31.0	388	64
4	64	61	6/36	7/6	19	11	20.5	32.5	228	111
5	65	66	3/60	6/6	29	7	20.5	31.5	604	94
6	47	48	6/18	6/6	36	4	21.0	31.0	844	10
7	61	61	6/12	6/6	23	8	27.5	33.0	712	72
8	64	65	6/74	7/6	32	7	24.0	30.5	392	111
9	54	54	6/18	6/6	28	9	27.0	30.5	384	30
10	67	68	6/60	7/6	24	9	27.0	30.5	296	160
11	69	70	6/74	7/6	34	7	35.0	30.5	376	140
12	58	58	6/12	6/6	18	4	30.0	31.0	116	24

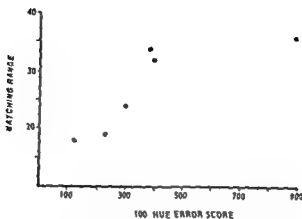


Fig. 1

A scattergram of matching range (ordinate) versus 100 Hue error score (abscissa)

range (Fig. 1). No significant correlation was present with the Spearman rank correlation test between the visual acuity and the 100 Hue error score ($\rho = +0.99$, $P > 0.05$) or between the visual acuity and the matching range ($\rho = +0.12$, $P > 0.05$).

Discussion

The results of the P-N anomaloscope and the I-M 100 Hue tests in tobacco amblyopia were correlated, i.e. the two tests were consistent with each other, thus confirming that both tests are useful in tobacco amblyopia.

Visual acuity affects colour discrimination (Jaeger 1956; François & Verriest 1961) but visual acuity alone probably was not responsible for the results on the anomaloscope in tobacco amblyopia as there was no significant relationship between visual acuity and the matching range.

With the P-N anomaloscope (Pukford & Lakowski 1960) the required colour defect in tobacco amblyopia is found to be of extreme protanomalous type. Like the 100 Hue score, the higher the matching range, the greater is the defect in colour discrimination and the more advanced is the disease. It is conceivable that in the early stages of tobacco amblyopia the defect starts as simple protanomaly and then progresses to extreme protanomaly and finally the defect may reach the dichromatic stage.

Acquired protanomaly has been described in receptor degeneration in the central retina (Pinckers 1972), in cone degeneration (Krill & Ishman 1971) and in some other retinal diseases (Jaeger 1956; François & Verriest 1961; Verriest

1963) whereas deuteranomalous defect is found in optic nerve diseases (François & Verriest 1961 Brill & Fishman 1971)

The site of defect in tobacco amblyopia is as yet not clear. Although the evidence in circumstantial, these findings confirm the defect in red sensitivity which has been suggested to reside in the retina (Schepens 1946 Mackenzie & Phillips 1968 Phillips Wang & Van Peborgh 1970). However a shift in the mid matching point as found in the present study does not provide evidence on the relative numbers of functioning red and green cones (Rushton & Baker 1964).

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ACQUIRED DYSCHRMATOPSIA IN SUCCESSFULLY TREATED RETINAL DETACHMENTS

BY

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The colour vision of 10 patients with successfully treated unilateral retinal detachment with macular involvement was tested with the Farnsworth Munsell 100 Hue test. A method has been described for inter eye comparison on the 100 Hue test error scores. In seven affected eyes the error scores were significantly worse at the 0.01 level of significance than those of their contralateral normal eyes. Three of the affected eyes had normal colour vision, two showed a Red Green colour defect, three showed a Yellow Blue colour defect and two were nonspecific. It is concluded that a retinal lesion can cause a RC colour defect in addition to the generally accepted YB and nonspecific colour defects. The uniocular dyschromatopsia is found to impair significantly ($P < 0.01$) the binocular vision when the patients' affected eye error scores and binocular error scores were compared with the uniocular and binocular error scores of age matched normal controls.

Key words: acquired dyschromatopsia - retinal detachment - Farnsworth Munsell 100 Hue test - tobacco amblyopia

It is generally stated that acquired dyschromatopsia is of three principal types: Red Green (RG) and Yellow Blue (YB) colour defects and an acquired dyschromatopsia without axis (Verriest 1963). The first is considered to be due

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to optic nerve disorders the second due to retinal lesions (François & Verriest 1957 1961 Cox 1960 1961 Verriest 1963) The third, unlike the first two is not a single entity and can arise from a variety of sources (Verriest 1963) However direct evidence of this classification is lacking and there is some doubt about these rigid divisions (Jaeger 1956 Krill & Fishman 1971 Dubois Poulsen 1972)

In retinal detachment the function of the sensory receptors is impaired presumably because of anatomical separation of the receptors from their nutritional bed After successful operation although the retina is reattached there may be some residual functional impairment either of visual acuity or of colour vision or both It seems reasonable to assume that these defects can be attributed entirely or mainly to a malfunction at the receptor level

The present study of acquired dyschromatopsia in retinal detachment has been undertaken to study

- a) the type and extent of colour defect in the affected eye
- b) the effect of a unocular acquired colour defect on binocular colour vision

(The underlying reason which suggested this study was the hypothesis that to bacco amblyopia was due to a lesion in the retina rather than in the optic nerve see Schepens 1946 Mackenzie & Phillips 1968 Phillips Wang & van Peaborg 1970 We then searched for a naturally occurring disease known to affect only the retina preferably in one eye only)

Patients and Methods

Patients were carefully selected and those who satisfied the following criteria were included in the study

- 1 Unilateral peripheral retinal detachment of rhegmatogenous nature and with macular involvement as colour vision is essentially a function of the macula

- 2 Normal contralateral eye
- 3 Not known to be suffering from systemic disease
- 4 Free from any congenital colour defect
- 5 Successful operation for retinal detachment and a minimum period of three months elapsed since the operation

Ten patients who were treated and followed up in the University Department at Manchester Royal Eye Hospital satisfied the above criteria

The Farnsworth Munsell 100 Hue test (Farnsworth 1943 1957) was used to test their colour vision as it is an extremely good test for acquired colour de

fects (François & Vernest 1961 Vernest 1963 Lakowski 1968 1969b Dubois Poulsen 1972) Not only does it detect the type of colour defect but also provides a measure of a person's ability to discriminate colour on a quantitative basis

The test consists of four boxes containing 85 circular discs painted with graded Munsell colours in matt finish to minimize directional reflection and mounted in bakelite caps The patient is presented with these coloured discs in a random fashion and he is required to arrange the discs in correct order of their colours between the fixed end caps in each box

From the patient's arrangement of caps his error score can be calculated The poorer the colour discrimination the more haphazard is the arrangement of caps and the higher is his error score The error score for each cap can also be plotted on a circular graph and a profile can be obtained

The shape of the profile gives the type of colour defect and is identified by bipolarity that is a clustering of maximum errors in two regions which are nearly opposite in the hue circle The line joining the two poles forms the axis of confusion which is different for different colour defects RG colour defects show maximum errors between the caps 56 and 10 and caps 12 to 26 whereas YB colour defects accumulate maximum errors around the cap 46 and around cap 1

The following procedure was adopted for subjecting the patient to the FM 100 Hue test

- 1 MacBeth Executive daylight lamp BBX 324 was used to provide standard uniform illumination

- 2 For each patient the initial test was always binocular The affected and the normal eyes were then similarly tested but the eye to be tested first was chosen at random by the toss of a coin In addition a random order of presentation of the four boxes in each test session was used

- 3 Between each test 10 min were allowed for rest and adaption to the light

- 4 No time limit was set to avoid racing against time

- 5 The error scores were plotted according to Kinnear's method (1970)

Results

Data and test scores of 10 affected eyes and their contralateral control eyes are given in Tables I and II The results of a control group matched for age are given in the last three columns of Table II

Classification of error scores: Criteria for normality

Some explanation of the classification system used in Table I is necessary. As regards the total error scores, colour vision and colour discrimination are age related in the general population (Iwakowski 1958, Verriest 1963). Verriest (1963) has calculated the mean and range of total error scores in different age groups in normal subjects so that the 95th percentile point for each age group can be used as a criterion of normality. On that basis, from Table I four eyes are definitely abnormal and one is on the borderline of normality. However, the additional information present from the score of the contralateral eye can be used as a more stringent criterion of normality. One way of determining such a criterion is by establishing norms for the size of the difference in error scores between the two eyes. If the presentation of the test to each eye is randomised, the expected mean of the differences will be zero. The mean of the differences was 1.8, which is not significantly different from zero. From Table II (control series) the standard deviation of the differences between the scores of each eye is 14. The 0.05 criterion point for the difference is therefore $1.96 \times 14 = 27$, and the 0.01 criterion point is $2.57 \times 14 = 36$. Thus the difference in error scores between normal eyes can be as large as 27 at the 0.05 probability level and 36 at the 0.01 level. By the use of the above criteria, it is assumed that a difference of 27 between eyes applies independently of the absolute score of either eye (i.e. given the score for one eye is 90, the upper limit for the score for the other eye is 57; given the score for one eye is 100, the upper limit for the score of the other eye is 127). However, because of the nature of the scoring system in the 100 Hue test, the distribution of error scores in a population does not conform to a normal distribution but is skewed (Kinnear 1970). This skewness is exaggerated in the present situation by the presence of a considerable age span in the control sample. It is to be expected therefore that the distribution of the differences in raw scores between eyes will also be skewed.

In addition to the requirement of a normal distribution, it is important in establishing norms to ensure that the raw score in any RI/II pair is independent of the size of the difference in raw scores between the two eyes, so that the correlation between the two approximates zero. For the control group, the correlation between the lower raw score in a RI/II pair and the size of the difference was $P = 0.65$ ($P < 0.05$). Therefore the higher the raw score, the bigger the difference in scores between eyes. The above criteria for differences in scores between eyes are therefore inappropriate because the size of the difference does depend on the absolute level of the raw score. As Kinnear (1970) has described, a square root transformation was performed on the data. The new correlation between the square root of the raw score and the size of the difference between the square root scores for each eye was $P = 0.03$.

Patient no	Age	Sex	Corrected VA affected eye	Corrected VA normal eye	Ictive error affected eye	Refractive error normal eye	Total score affected eye	Total score normal eye	Colour affected eye	Type of colour defect normal eye
1	12	M	C/24	6/5	+ 1.0 sph + 0.50 cyl 180°	- 0.75 ph + 0.50 cyl 165°	304	92	YG	N
2	12	F	6/18	6/4	+ 1.0 cyl 90° - 6.75 sph	+ 0.75 sph - 6.50 sph	19	16	N	N
3	17	M	C/12	6/5	+ 1.50 cyl 90° + 0.0 cyl 90°	+ 1.75 cyl 90° 0	88	4	RG	N
4	21	M	6/5	C/4	1.75 sph	- 1.05 sph	49	90	N	N
5	28	M	C/18	6/5	- 12.0 sph - 3.75 cyl 180°	- 14.0 sph + 2.0 cyl 16°	16	10	N	N
6	47	M	6/24	6/9	+ 0.50 sph + 0.50 cyl 75°	+ 0.50 ph + 1.0 cyl 30°	240	144	YB	NS (borderline)
7	51	M	6/12	C/5	+ 0.75 sph + 0.50 cyl 170°	+ 0.50 ph + 0.50 cyl 170°	116	96	NS	N
8	55	M	6/10	6/4	+ 1.75 sph + 0.75 cyl 180°	+ 1.75 sph + 1.00 cyl 50°	93	96	YB	N
9	67	M	6/10	C/5	+ 1.0 sph + 0.75 cyl 45°	+ 1.0 sph + 0.50 cyl 180°	449	124	NS	N
10	80	M	6/10	C/5			173	60	YB	N

RG = Red Green

YB = Yellow Blue

NS = Nonspecific

N = Normal

Classification of error scores Criteria for normality

Some explanation of the classification system used in Table I is necessary. As regards the total error scores colour vision and colour discrimination are age related in the general population (Iwakowski 1958 Verriest 1963). Verriest (1963) has calculated the mean and range of total error scores in different age groups in normal subjects so that the 95th percentile point for each age group can be used as a criterion of normality. On that basis from Table I four eyes are definitely abnormal and one is on the borderline of normality. However the additional information present from the score of the contralateral eye can be used as a more stringent criterion of normality. One way of determining such a criterion is by establishing norms for the size of the difference in error scores between the two eyes. If the presentation of the test to each eye is randomised the expected mean of the differences will be zero. The mean of the differences was 1.8 which is not significantly different from zero. From Table II (control series) the standard deviation of the differences between the scores of each eye is 14. The 0.05 criterion point for the difference is therefore $1.96 \times 14 = 27$ and the 0.1 criterion point is $2.57 \times 14 = 36$. Thus the difference in error scores between normal eyes can be as large as 27 at the 0.05 probability level and 36 at the 0.1 level. By the use of the above criterion it is assumed that a difference of 27 between eyes applies independently of the absolute score of either eye (i.e. given the score for one eye is 30 the upper limit for the score for the other eye is 57 given the score for one eye is 100 the upper limit for the score of the other eye is 127). However because of the nature of the scoring system in the 100 Hue test the distribution of error scores in a population does not conform to a normal distribution but is skewed (Kinner 1960). This skewness is exaggerated in the present situation by the presence of a considerable age span in the control sample. It is to be expected therefore that the distribution of the differences in raw scores between eyes will also be skew.

In addition to the requirement of a normal distribution it is important in establishing norms to ensure that the raw score in any RI/LE pair is independent of the size of the difference in raw scores between the two eyes so that the correlation between the two approximates zero. For the control group the correlation between the lower raw score in a RI/LE pair and the size of the difference was $P = 0.65$ ($P < 0.05$). Therefore the higher the raw score the bigger the difference in scores between eyes. The above criterion for differences in scores between eyes are therefore inappropriate because the size of the difference does depend on the absolute level of the raw score. As Kinner (1960) has described a square root transformation was performed on the data. The new correlation between the square root of the raw score and the size of the difference between the square root scores for each eye was $P = 0.03$.

tralateral normal eye scores by the Wilcoxon matched pairs test the result was significant ($P < 0.01$) (The scores of the affected eyes were significantly higher than the scores of the normal eyes)

Of the seven colour defective eyes two showed a RC colour defect three showed a YB colour defect and two showed a non specific colour defect The borderline case in the normal eye was of the non specific type It was of interest to note the difference in the type of defect in the younger and older age group The two RG defects occurred in patients under 20 years the three YB defects occurred in patients over 45 years However the numbers are too small to permit any firm conclusions to be drawn

■ The effect of a unocular colour defect on binocular colour vision

To evaluate this effect 10 normal controls matched for age were also tested by the same procedure as was used on the patients The results are shown in Table II

The initial hypothesis that a unocular colour defect does *not* affect binocular colour vision was tested in the following way For each *patient* the difference in error score was obtained between the binocular score and the normal eye score For each control subject the difference in error score was obtained between the binocular score and the normal eye occupying the same position in the test sequence i.e. 1st or 2nd as the normal eye of the matched patient (Note that the binocular test was always given first to both groups) The two sets of differences were compared by the Wilcoxon matched pairs test which was significant ($P < 0.01$) The difference between the two scores for the patients was greater than the difference between the two scores for the controls As no significant difference existed between the normal eye scores of the two groups (i.e. they were indeed matched so that the defect was unocular) the difference arises from the relatively poorer *binocular* performance of the patients

The original hypothesis was therefore rejected and it was concluded that a *unocular* colour defect *does* impair *binocular* colour vision

One factor which might be related to this finding (and which was not taken into account) was eye dominance It may be the case that if the affected eye is the dominant eye then binocular colour vision is impaired but if the affected eye is the non dominant eye then binocular colour vision is unaffected With regard to this it is worth noting that seven of the affected eyes were *right* eyes so that if there is a greater probability of right eyes being dominant then there is a possibility that the affected eyes are the dominant eyes in this sample If this is the case the conclusion may not apply in those patients where the unocular defect is in the non dominant eye

which was not significant. Thus the size of the difference was now independent of the absolute score. As Kinnear (1970) points out, it should not be assumed that there is a special relationship between a square root transformation and the nature of the 100 Hue test. It just happens to be most appropriate transformation in the present case as it was for Kinnear's diabetic data.

The new standard deviation of the difference in square root scores for each eye is 1.01 and the new limits for the difference between eyes are $1.96 \times 1.01 = 1.97$ for the 0.05 level and $2.57 \times 1.01 = 2.58$ for the 0.01 level (Tolerance limits are 2.4 and 3.4 respectively). It should also be emphasised that both control and experimental groups had a binocular test first followed by a random decision for the two subsequent monocular tests. A Wilcoxon Matched Pairs test showed no significant difference between the results of the first monocular test and the second monocular test. Thus there is no restriction on the sign of the difference in scores between the eye tested first and the eye tested second.

However, this does not imply that if the binocular test had not been present there would not have been a significant difference between the eye tested first and the eye tested second because of the possibility of a learning effect. Consequently, if the scores for each eye are to be compared when an initial binocular test has not been given, randomising the box presentation alternately to each eye is recommended, i.e. the RL does the 1st, 3rd, 5th, 7th boxes and the LE does the 2nd, 4th, 6th, 8th boxes - no single box being presented consecutively to each eye.

This procedure for enabling comparisons between eyes is necessary for handling the present data and illustrates a method which might be extended to other studies. Clearly a standard deviation based on 10 observations is hardly sufficient for general norms. Nevertheless, in application of this principle enables more stringent criteria to be established for inter-eye comparisons (Aspinall 1973).

A. Comparison between normal and affected eyes

There are seven definitely abnormal and one borderline case in Table 1 as judged by the absolute error score and the difference in transformed error scores between eyes. (As an example, note patient No. 3. An error score of 88 is well within normal limits for his age group. However, by the new criteria the square root scores are 2 and 9.4 for each eye. This difference (7.4) is greater than 3.4, which is the 0.01 level criterion for abnormality.) All the abnormal eyes on colour discrimination are the affected eyes, the borderline case being in the normal eye. When the affected eye scores were compared with the con-

Discussion

The results of this study differ from the orthodox view that retinal lesions produce YB colour defects. In addition to YB defects both RG defects and non-specific defects have been found. A variety of dyschromatopsias have been observed in retinal detachment. François & Verriest (1957, 1961), Verriest (1963) and Koliopoulos & Theodosiadis (1962) all report YB defects in retinal detachment. On the other hand Cox (1960, 1961), Gaillard (1962) and François & Verriest (1968) found both YB and RG defects.

In some of the studies there were no matched controls, full details of the patients were lacking and visual acuities were low. Although visual acuity can influence colour vision (Jaeger 1956), persons with reduced visual acuity can be satisfactorily examined with the 100 Hue test (François & Verriest 1961). Visual acuity could not have been a major factor in our results as six of our patients had acuities of 6/12 or better and the two patients with a slightly poorer acuity of 6/18 showed no colour defect at all. Moreover, there was no significant correlation in the patients between the visual acuities and the total error score.

François & Verriest (1957, 1961) thought that the YB defect might be merely due to pre-existing myopia gravis and in their later study (1968) they report that cases of myopia show a YB defect (probably due to myopia itself) whereas non-myopic cases show a defect without predominant axis or a type I RG defect. In fact the authors consider that this latter defect is the typical defect of retinal detachment.

In our series myopia of $-12.00/-3.25$ cyl may be the explanation for one YB colour defect (patient No. 6 in Table I). Most of the other patients (7 out of 10) had minor degrees of hypermetropia. These other cases confirm that a RG defect does occur in successfully treated (surgically) cases of retinal detachment, which finding is also consistent with Pinckers' (1972) statement that RG colour defects (protanomaly) are found in diseases where receptors at the posterior pole degenerate.

It should be pointed out that if the defect manifested itself simply as congenital protanomaly it would not be discernible on the 100 Hue test as the test was not designed to detect simple anomalous trichromatism. However, both RG and YB profiles have been clearly distinguishable in the non-myopic patients of our group. One question which arises is whether the different dyschromatopsias are representative of different stages of the condition so that one defect may progress to another. Normal ageing processes produce colour vision losses of the YB type (Lakowski 1958, Verriest 1963) and some diseases can cause these changes prematurely (Lakowski 1969a). One possible explanation of the YB colour defect found in our older patients is that the normal ageing

Table II
 Farnsworth Munsell 100 Hue test raw and transformed scores of 10 patients and 10 normal controls The figures in brackets are the square roots of the raw scores

No	Age		Patients Error Scores				Control Error Scores		
	Patient	Control	Affected eye	Normal eye	Binocular		Random 1st eye	Random 2nd eye	Binocular
1	12	12	304 (17.4)	92 (9.6)	108 (10.4)		64 (8.0)	48 (6.9)	60 (7.8)
2	12	12	12 (3.5)	16 (4.0)	12 (4.0)		28 (5.3)	16 (4.0)	16 (4.0)
3	17	19	88 (9.4)	4 (2.0)	16 (4.0)		20 (4.5)	28 (5.3)	20 (4.5)
4	21	20	48 (6.9)	20 (4.5)	36 (6.0)		12 (3.5)	16 (4.0)	4 (2.0)
5	28	28	16 (4.0)	16 (4.0)	12 (3.5)		4 (2.0)	8 (2.8)	4 (2.0)
6	47	48	240 (15.5)	144 (12.0)	168 (13.0)		12 (3.5)	12 (3.5)	0 0
7	51	50	116 (10.8)	36 (6.0)	44 (6.6)		20 (4.5)	48 (6.9)	20 (4.5)
8	65	65	222 (14.9)	96 (9.8)	140 (11.8)		88 (9.4)	82 (9.1)	76 (8.7)
9	67	67	448 (21.2)	124 (11.1)	144 (12.0)		140 (11.9)	128 (11.3)	116 (10.8)
10	10	10	172 (13.1)	60 (7.8)	76 (8.7)		188 (13.7)	172 (13.1)	156 (12.5)

Acknowledgement

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process is accelerated and accentuated as a result of disturbance in the function of the neuroreceptors in retinal detachment. If the YB mechanism is most unstable and most readily affected in retinal pathology, then RG defects may appear at a more advanced stage. Thus although the 100 Hue test may indicate a predominantly RG profile it should nevertheless be possible to demonstrate a YB defect over the appropriate cups. Similarly a YB defect may contain RG errors. Of the YB defects recorded in the older patients one is made up of errors in the YB region only. The other two while predominantly YB do include RG errors.

The RG defects in the younger patients are more difficult to explain and the sequence of change suggested above no longer holds. One patient has an RG profile with concomitant errors in the YB region. However the other patient (No 3) has an RG profile without the presence of an error greater than two in the YB region here then as given by the test is an RG defect without an associated YB defect.

Thus the presence of an RG defect without associated YB errors and a YB defect without associated RG errors points to two qualitatively different types of visual loss in retinal detachment. This difference does not seem to rest on the myopic/non myopic division.

Conclusions

A method has been outlined for inter eye comparison on the 100 Hue test. This together with the standard norms of Verriest (1963) has been applied to a group of successfully treated cases (surgically) of retinal detachment.

Three months after treatment the results from affected eyes were significantly worse than those from unaffected eyes. Three of the affected eyes had normal colour vision, two showed an RG colour defect, three showed a YB colour defect and two showed a non specific colour defect. Accordingly there is evidence that a purely local retinal lesion can cause an RG defect (as well as the generally accepted YB and non specific defect - and no defect at all!)

This gives some support albeit very indirect for the hypothesis that a retinal lesion could be the cause of tobacco amblyopia. The presence of each type of defect in isolation suggests two qualitatively different types of visual loss in retinal detachment. This difference may or may not rest on the myopic/non myopic division (François & Verriest 1968).

The existence of a uniocular dyschromatopsia was found to impair binocular colour vision. The role of eye dominance in this relationship awaits further investigation.

LASER PERIMETRY
DIAGNOSTIC APPLICATION IN SIX CASES OF
PITUITARY CHROMOPHOBE ADENOMA

BY

F. BARTOLI AND L. LIUZZI

An apparatus consisting of a Goldmann perimeter fitted with a laser generator is described. Sharper definition and earlier detection of defects with this technique in six cases of chromophobe adenoma are reported.

Key words: pituitary gland - chromophobe adenoma - perimetry laser

Coloured light perimetry has been much criticised in the past. An attempt has therefore been made to provide an apparatus capable of generating a type of coloured light to which such criticism would not apply. Comparison has also been made with traditional perimetry to see whether this type of light gives better results.

The physiological premises for correct coloured light perimetry were first established and then applied to the construction of a suitable apparatus (). One main objective was a standardisable and hence essentially monochromatic stimulus. This was achieved by using a laser (i.e. a generator and amplifier of monochromatic radiations) with a Goldmann perimeter. For reasons given elsewhere, a continuous laser was employed. This was a helium neon laser with an emission band in the red region (6328 Å).

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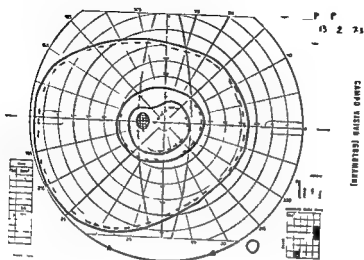


Fig 1a

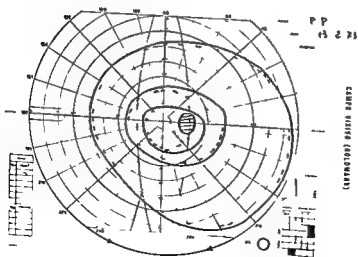


Fig 1b

A series of filters was used to obtain 40 luminance levels. Positive and negative lenses were also interposed to increase or decrease the area of the projected target. The apparatus has the following technical features: wavelength 6928 Å, band width 0.1 Å (i.e. strictly monochromatic), maximum power 0.5 mW (i.e. well below the so called lesion threshold: the light is also filtered repeatedly, as already mentioned), width of beam 0.8 mm, spread 1 milliradian.

Technique

Determination of the visual field was done with the Goldmann perimeter. We have already used this method in kinetic perimetry. Both white light and the laser were employed to obtain comparative data. Objective assessment was ensured by looking for isopter coincidence. If for example determinations were first carried out with white targets, laser readings were then obtained with isopters perfectly superimposed on the white isopters in the supposedly unimpaired area. The large number of brightness levels provided by the apparatus made this easy to accomplish.

The most effective method of course is that which gives the earliest and most precise evidence of defects. The possible influence of artefacts on our method was guarded against by following the progress of defects first detected with the laser. One example of this follow-up is illustrated in the cases reported below. It was found that white light evidence of visual field impairment was eventually obtained from laser detected areas. In the case of progressive chromophobe adenoma we observed that detection could be anticipated by some 40 to 50 days.

The series reported here consists of six cases of chromophobe adenoma subjected in random order to both white light and laser perimetry after a few hours rest to prevent fatigue.

Case 1

Pasqualina P. recurrence of chromophobe adenoma treated by means of ^{131}Au implantation in March 1971. Recrudescence of headaches.

Vision 00/10/10 without glasses and normal ophthalmoscope picture.

Visual field (Fig. 1)

- OD white light (continuous line) slight flattening (inner isopter) laser (broken line) flattening in upper temporal quadrant (middle isopter) and hemianoptic defect (inner isopter)
- OS white light slight notch in upper temporal quadrant (inner isopter) laser upper temporal quadrant optic defect (inner isopter) and slight notch (middle isopter)

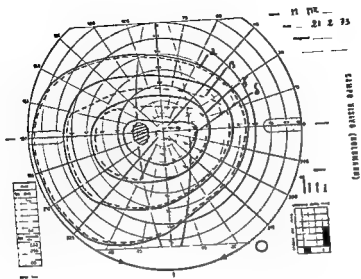


Fig 9a

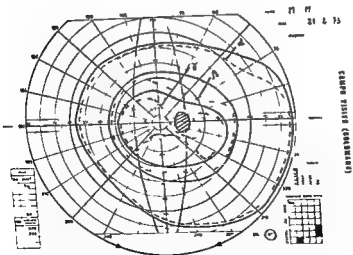


Fig 9b

Case 2

Maria Rosa M 52 years admitted to Turin University Endocrine Surgery Centre for possible surgical management of chromophobe adenoma

Vision OD 8/10 without glasses and normal ophthalmoscope picture

Visual field (Fig 2)

OD white light (continuous line) flattening in upper temporal quadrant (inner isopter)

laser (broken line) upper temporal quadrant defect (peripheral isopter) confirmed and enlarged in association with a lower temporal quadrant defect in the other isopters

OS white light flattening (central isopter)

laser flattening with lower temporonasal defect (middle isopter) and hemianoptic defect (inner isopter)

Case 3

Ines B 32 years admitted to the Turin University Endocrine Surgery Centre with chromophobe adenoma

Vision — 10/10 without glasses and normal ophthalmoscope picture

Visual field (Fig 3)

OD white light upper temporal quadrant defect (central isopter) laser horizontal defect (middle isopter) Only part of the central and lower nasal regions preserved in the inner isopter

OS white light upper temporal quadrant defect (inner isopter)

laser small upper temporonasal defect (middle isopter) is seen to be of greater extent in the inner isopter

Case 4

Crisceppina P 46 years admitted to the Turin University Neurological Clinic for left palpebral ptosis associated with left mydriasis and marked frontal orbital pain. Radiography showed a wide sella with a double floor coupled with straightening and wear of the dorsum. Ophthalmological and campimetric examination for suspected chromophobe adenoma was requested

Vision OD 7-8/10 and OS 1/10 without glasses and normal ophthalmoscope picture.

Visual field (Fig 4)

OD white light notch in upper temporal quadrant (inner isopter)

laser slight defect (middle isopter) seen to be horizontal in the inner isopter

OS white light within the limits of normal

laser horizontal defect (inner isopter)

Case 5

Annalisa M 35 years operated for chromophobe adenoma via the transnasosphenoid route at the Milan University Neurological Clinic (March 1981). Cycle of 15 telecobalt treatments at S Giovanni Hospital Turin completed July 1981. Admitted to the Turin University Endocrine Surgery Centre

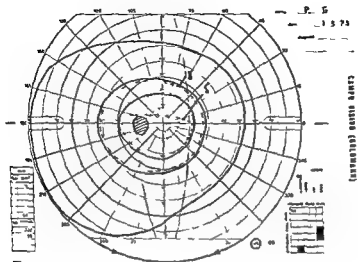


Fig 4a

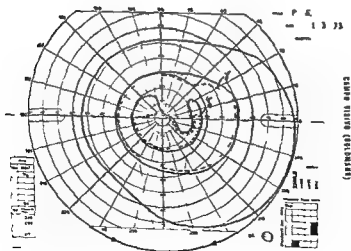


Fig 4b

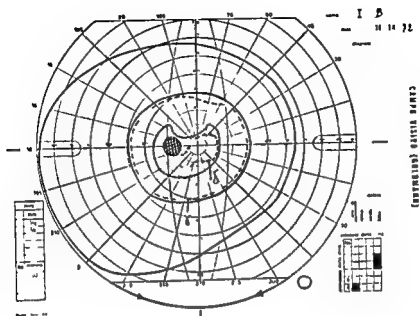


Fig 3a

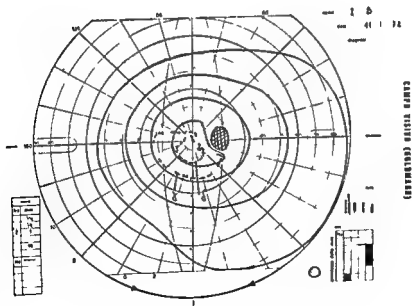


Fig 3b

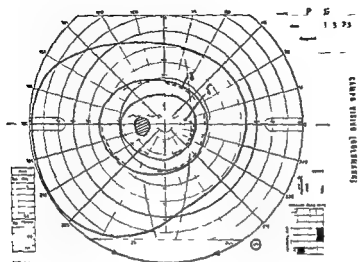


Fig 4a

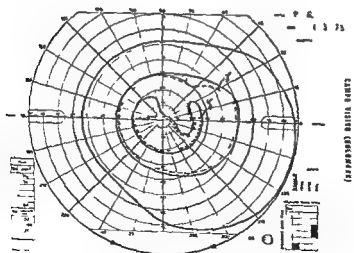


Fig 4b

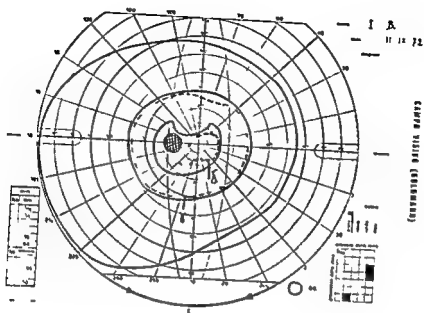


Fig 3a

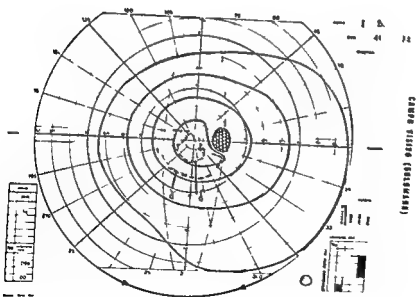


Fig 3b

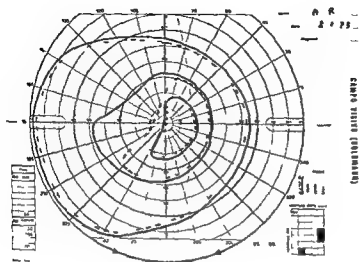


Fig 6a

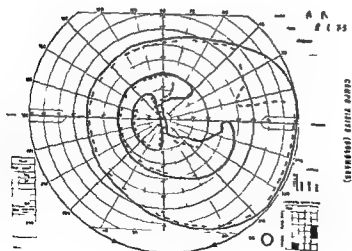


Fig 6b

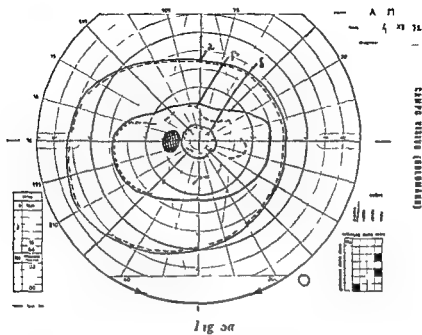


Fig 5a

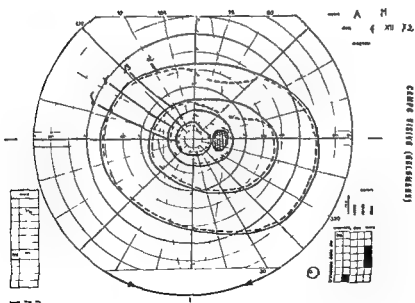


Fig 5b

Vision 00 10/10 without glasses and normal ophthalmological picture

Visual field (Fig 5)

OD white light restriction (all isopters) upper temporal quadrant defect (inner isopter)
laser upper temporal quadrant defect (all isopters)

OS white light concentric restriction and flattening in the upper quadrants (middle isopter) irregular defect (inner isopter)
laser irregular defect also detected in middle isopter

Case 5

Adelina R. 47 years following referral from the neurological division of the Biella Hospital with suspected chromophobe adenoma admitted twice for campimetric examination and subsequently operated

1st examination (8/1/78)

Vision 00 8-9/10 and normal ophthalmoscopic picture

Visual field (Fig 6)

OD white light notch in upper and lower temporal quadrants (middle isopter) temporal hemianoptic defect (inner isopter)
laser defect present in peripheral isopter and increasingly evident towards the inner isopter

OS white light upper temporal flattening (middle isopter) hemianoptic defect (inner isopter)
laser more extensive defect tending towards temporal hemianopsia

2nd examination (about 40 days later)

Vision 00 5-6/10 without glasses

Ophthalmoscope slight temporal pallor of both discs

Visual field (Fig 7)

OD white light defects more pronounced and picture similar to that observed with the laser at the 1st examination (all isopters)
laser defects still more pronounced (all isopters)

Conclusions

It was clear in all six cases that there was a marked difference between white light and laser examination in the revelation of visual field defects. These were readily detected and more easily interpreted with the laser. Furthermore the latter revealed defects in isopters that appeared unimpaired on conventional examination. The last case is of particular interest in this respect since white light confirmation of solely laser detected impairment was obtained during a second examination after an interval of 40 days.

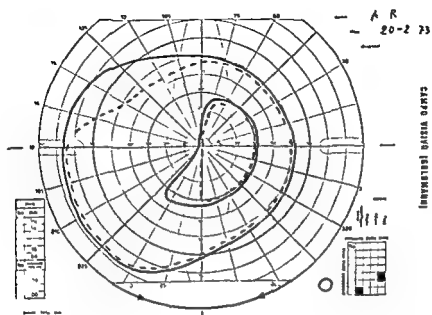


Fig 7a

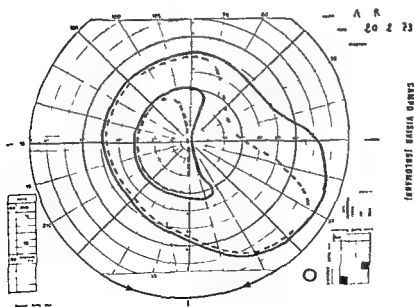


Fig 7b

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EXPERIMENTAL IRIS SUTURES IN THE MONKEY

BY

B EHINGER and E PALM

Artificial iris wounds were sutured with 90 μ m monofilament nylon sutures in 15 monkey eyes and studied histologically at different intervals up to 6 months

The monkey iris does not form any scars. When two wound lips are apposed by exact suturing they join. The mechanical strength of the union is as yet unknown. The iris reacts to the operation but not enough to preclude the procedure. There is no adverse late reaction to the suture material (80 μ m monofilament nylon) for at least 3 months after the operation.

Key words: iris sutures, surgery - monkey

A universal clinical experience is that defects in the iris are not usually repaired but remain open for decades forming permanent communications between the chambers of the eye and that little or no scar tissue is formed (Duke Elder 1966). Modern technique (operating microscope and ultrafine suture material) has made refined interventions of the iris possible and suturing of the iris is now practised as a routine in many centres (Mackensen 1969, Mackensen, Custodis & Raptis 1972, Harms 1972). Because little is known about the reaction of the iris to this surgery the present study was undertaken.

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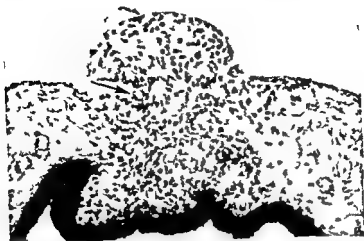


Fig 2

Iris 6 days postoperatively. There is a considerable accumulation of heavily pigmented clump cells and a moderate infiltration of inflammatory round cells. There is little or no special reaction around the suture (arrow). The wound lips have joined and their edges are not readily identifiable. Haematoxylin and eosin $\times 100$.

after surgery a normal or almost normal pupillary light reaction could be seen. In most cases a slight to moderate iris atrophy in the suture area was noted with some loss of pigment epithelium (Fig 1). A more pronounced general and macroscopically visible iris atrophy with loss of both stroma and pigment epithelium was seen in two eyes; these subsequently proved to contain peripheral anterior synechiae and in one instance also a microabscess. No cataracts were found.

Microscopic Examination

In the early period (4 or 16 days after the operation) the iris showed a moderate round cell infiltration near the iris wound. So called clump cells of Koganei (see Duke Elder 1961 or Wobmann & Fine 1979) were already apparent (Fig 2). After 1 month little or no inflammatory reaction was visible in the sections (Fig 3). Even after 6 months the irides were without inflammatory reaction. The clump cells were fewer but were still present (Fig 5). There was no scar formation or any sign of regenerative activity. Wound lips that had not been brought in contact with each other were slightly rounded off

Material and Methods

Twelve eyes in cynomolgus monkeys (*cynomolgus irus*) were used. They were opened under an operating microscope by a corneal 140° incision. A radial cut was made from the iris root to the pupil with a pair of scissors at 12 o'clock and then sutured with two stitches of 30 μ m monofilament nylon (Tubinger Nahtmaterial Klein). The corneal wound was closed with 3-5 interrupted sutures. If necessary the iris was gently repositioned and the anterior chamber was re-filled with 0.9% NaCl and a small air bubble. No operative complications were encountered and the immediate postoperative course was uneventful. No hemorrhages or flat chambers were observed.

The eyes were examined at regular intervals by ordinary clinical methods. At different time intervals after the operation the animals were sacrificed and all the eyes serially sectioned and studied by histological routine methods.

Results

Macroscopic examination

There was a slight postoperative inflammation but it subsided spontaneously within 2 weeks. In all cases the pupil was round or nearly round. A few days

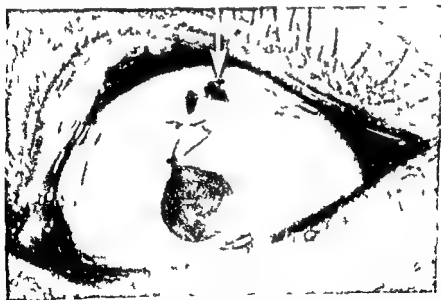


Fig 1

Cynomolgus monkey experimental iris suture 3 months after the operation. The two stitches can be seen in the iris at 12 o'clock. The original incision has remained open at the iris base. To the right of it the iris has atrophied (arrow) and there is also some atrophy at the stitches particularly at the nasal side (topmost).

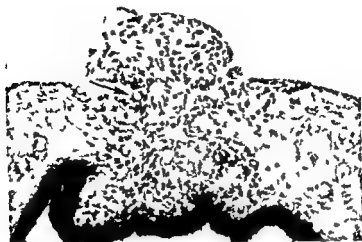


Fig 2

Iris 6 days postoperatively. There is a considerable accumulation of heavily pigmented clump cells and a moderate infiltration of inflammatory round cells. There is little or no special reaction around the suture (arrow). The wound lips have joined and their edges are not readily identifiable. Haematoxylin and eosin $\times 105$.

after surgery a normal or almost normal pupillary light reaction could be seen. In most cases a slight to moderate iris atrophy in the suture area was noted with some loss of pigment epithelium (Fig 1). A more pronounced general and macroscopically visible iris atrophy with loss of both stroma and pigment epithelium was seen in two eyes; these subsequently proved to contain peripheral anterior synechiae and in one instance also a microabscess. No cataracts were found.

Microscopic Examination

In the early period (7 or 16 days after the operation) the iris showed a moderate round cell infiltration near the iris wound. So called clump cells of Koganei (see Duke Elder 1961 or Wobmann & Fine 1972) were already apparent (Fig 2). After 1 month little or no inflammatory reaction was visible in the sections (Fig 3). Even after 6 months the irides were without inflammatory reaction. The clump cells were fewer but were still present (Fig 5). There was no scar formation or any sign of regenerative activity. Wound lips that had not been brought in contact with each other were slightly rounded off.

otherwise they had the same appearance as fresh cuts. Two eyes 7 and 30 days after the operation showed a marked iris atrophy as observed already macroscopically. In both these cases the microscopic examination revealed extensive anterior synechiae to the corneal wound; one of the irides also had a microabscess around a suture (Fig. 6). The nylon sutures in the iris were easily seen in the sections. There was no tissue reaction around them (Figs. 2 and 3). Apart from the above described microabscess, no necroses were observed. The iris wound apparently healed rapidly with cellular continuity apparent in the stroma already after one week (Fig. 2). However, as already noted, there was no scar formation. Mitoses or other signs of proliferation were



Fig. 3

Iris 1 month postoperatively. The knot is visible. The iris has broken in the histotechnical preparation and the break seems to be in the position of the original incision. The number of clump cells has decreased compared with Fig. 1. There is no inflammatory reaction. Haematoxylin and eosin $\times 120$.

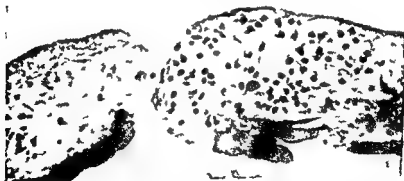


Fig. 4

Iris wound sutured 3 months previously. Section taken near a remaining hole in the iris. A fine tissue bridge can be seen between the wound lips, but there is no sign of active regenerative repair. The wound edges have become slightly rounded off. There is a persistent loss of pigment epithelium. Haematoxylin and eosin $\times 120$.



Fig 5

Iris sutured 6 months previously. The pigment epithelium has become intercalated in the wound and prevented healing. There are some remaining clump cells but otherwise no signs of tissue reaction, nor is there any sign of regenerative repair. Haematoxylin and eosin $\times 190$.

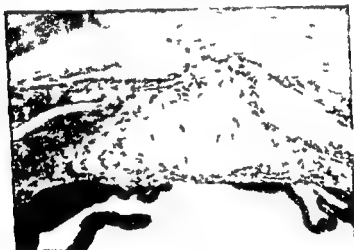


Fig 6

The microabscess around the suture knot in one of the eyes. There are also anterior synechiae. Haematoxylin and eosin $\times 75$.

rare in contrast with the findings by Calvin & Roy (1972). Instead the ordinary iris stromal cells seemed to join each other directly with little or no fibrillar intercellular material. The mechanical strength of such a union cannot be assessed from the microscopical appearance but apparently it is reduced

as in the sections the union tended to break even (see Fig 3) after 6 months of healing. If there was a gap in the wound no healing took place (Fig 4). Even small dehiscences in the iris (down to about 50 μ m) remained intact macroscopically throughout the observation period and microscopic examination failed to reveal any signs of regenerative activity (cf Figs 4 and 5). When pigment epithelium lay in the iris wound separating its two lips it seemed to prevent healing (Fig 5).

Discussion

In rabbits a weak tendency for healing was noted by Daniel (1944) after iridectomy. Small linear incisions in the rabbit iris were noted to heal spontaneously (Paragno 1934 cited by Daniel 1944) as Calvin & Roy (1972) have recently confirmed. When iridotomies were sutured in rabbits they healed with some scar formation (Witmer & Reme 1972).

However rabbit ocular tissues behave quite differently from those of primates. Even minor interventions on the rabbit eye result in a pronounced protein exudation into the aqueous with formation of extensive fibrin clots which may initiate scar formation (cf Hogan & Zimmerman 1962). Such clots are rare in primates. The general ocular tissue reaction to trauma is also much more pronounced in rabbits than in primates. Thus it is important to experiment with monkeys in order to obtain results as applicable to humans as possible. No such studies were available when the present work began but have recently and independently been performed by Witmer & Reme (1972) and Luntz Krufmann & Spiller (1972). The reaction of the human iris to iridectomy and iridotomy has been studied by Duke Elder (1966). It is generally agreed that there is no or only a slight tendency for the human iris to heal although Teng Chai & Kertzin (1962) reported some instances of slight reparative activity of the cut edges of the iris (but on proper healing with union of the wound lips). The pigment epithelium of the iris also reacts very little to injury (Norn 1968). There is no migration of epithelial cells along the iris surface to fill in defects such as can be seen in e.g. the cornea.

The present study confirms that there is essentially no scar formation in the monkey iris. However when the two wound lips of the cut iris are joined mechanically by stitches they apparently form cellular bridges.

Because of the low capacity to form scars the healing ability of the monkey iris is small. It is prevented if pigment epithelium cells become interposed between the wound lips. The iris is apparently also unable to fill out even a very small dehiscence. The results agree closely with those reported by Witmer &

Remé (1970) and by Luntz et al (1972) Clearly if healing of the iris is the intention meticulous care must be exercised to appose the wound lips perfectly leaving no tissue gaps and no pigment epithelium interposed in the wound This may matter little if permanent sutures are relied on but it is important if resorbable sutures are used

All cases studied revealed a slight immediate inflammatory reaction with some plasma cells and polymorphs this reaction subsided in about 2 weeks So called clump cells of Hoggan (see Duke Elder 1961 or Wobmann & Fine 1972) appeared rapidly close to the suture They persisted throughout the observation period (6 months) although in decreasing numbers There were no signs of necrosis except where there was an abscess around a suture In all cases there was also a moderate iris atrophy in the region of the wound In two cases the entire iris had atrophied Here extensive anterior synechiae were present However we saw no bleedings in any iris as Luntz et al (1972) did Obviously the iris reacts to the suturing trauma but the reaction is not so adverse as to preclude this operation The iris muscles retain their ability to promptly regulate the pupil size

As the suture material has to be left in the eye it is necessary to know its long time effects Apart from the immediate reaction to the surgical trauma there is nothing to suggest any adverse reactions to the nylon suture The eyes were quiet throughout the observation period when the immediate trauma had subsided Histologically there was no reaction around the sutures either inflammatory or allergic Results in agreement have recently been published (Witmer & Remé 1970 Luntz et al 1972 Rich & McPherson 1972)

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ULTRASONIC EXAMINATIONS OF FOREIGN BODIES IN THE POSTERIOR WALL OF THE EYE

BY

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Eyes to be enucleated due to intraocular tumor or absolute glaucoma were used in an ultrasonic investigation of foreign bodies situated retrolaterally or in the choroid scleral complex. The echograph findings of four intra choroidal, five intrascleral and three retrolateral foreign bodies were demonstrated. The foreign bodies were of iron and were polygonal in shape. The intrachoroidal foreign bodies weighed 0.081–0.321 mg, the intrascleral 0.120–0.695 mg and the retrolateral 0.787–1.456 mg. In cases where double perforation was suspected and where the ocular media are turbid ultrasonography would appear capable of giving valuable information as to whether a foreign body is located intra- or extraocularly.

Key words: ultrasound – ocular foreign bodies

The use of ultrasonography as a diagnostic tool for the detection of intraocular foreign bodies including those that do not appear on an X ray has been described by many authors (Oksala 1959, 1960, Bronson 1964, 1965, 1966, Penner & Passmore 1966, Runyan & Penner 1969, Coleman & Trokel 1971, Cowden & Runyan 1971).

Based on a paper read at the meeting of The Norwegian Ophthalmological Society, Bergen, Norway, May 22–26, 1973.

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Localization of foreign body

Intrachoroidal

Intrascleral

Retroscleral

1 - 4

5 - 9

10 - 12

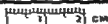


Fig 1

Photograph of the foreign bodies (iron) in scale 1 : 1

on the desired spot behind the equator after the bulbus had been turned over at the muscle attachments by means of hooks. The intraocular foreign bodies were placed in the choroid through a small incision in the sclera and were pushed into place with a forceps (Eyes with tumors were not used for foreign bodies with this localization). The intrascleral foreign bodies were placed in a small unperforated incision in the sclera, the retroscleral bodies as close to the scleral wall as possible. After the eye had regained a natural resting position the ultrasonic investigation was made with a Kretztechnik ultrasonograph model 7200 MA and an 8 MHz/5 mm plane transducer (NM 8-5 k). The examination was carried out transsclerally in the normal manner with the transducer in direct contact with the sclera. The apparatus was first set at a sensitivity level of 30 db and the foreign body sought by constantly moving the

Table 1
Weight of foreign body (iron) in mg

No	Intra choroidal weight	No	Intrascleral weight	No	Retroscleral weight
1	0.041	5	0.100	10	0.787
2	0.307	6	0.574	11	0.763
3	0.153	7	1.159	12	1.450
4	0.316	8	0.635		
		9	0.310		

When double perforation is suspected and the ocular media are turbid it is often difficult to establish by X-ray examination whether the position of a foreign body is intra- or extrabulbar. This also applies when special X-ray techniques such as the Comberg-Pfeiffer method are employed if the foreign body is located in the vicinity of the posterior bulbar wall. The localization of foreign bodies by these methods is based on the mean values of the axial length of the eye. Individual variation in the size of the eye occurs quite often however and it therefore usually is not possible to determine whether a foreign body with this localization is inside or outside the globe (Cernet & Hennewig 1966). In the case of foreign bodies located within the retinal-choroidal-scleral complex there appear to be diverging opinions as to the diagnostic value of ultrasonography (Nover & Stallkamp 1962, Oksala & Salminen 1966, Ossoinig & Scher 1969, Runyan & Penner 1969, Coleman & Trokel 1971). However the consensus of opinion appears to be that foreign bodies in this area can be detected by ultrasonography with only slight inaccuracy if any.

In one experimental examination *in vitro* (Larsen & Cjeruldsen 1973) it was found that even relatively small foreign bodies located in the posterior bulbar wall could be detected by ultrasonography. It would seem to be beyond doubt however that the biological structures in and around the bulb are capable of altering the character of the ultrasonogram when blood circulation has ceased and the temperature in the tissue is no longer physiological. The findings in this experiment and in corresponding living eyes therefore do not need to be identical. The object of the present study was by *in vivo* examination to throw further light on the problems of ultrasonic detection of foreign bodies located in or near the posterior bulbar wall.

Material and Methods

This investigation used 11 eyes due to be enucleated because of absolute glaucoma or intrabulbar tumor. Foreign bodies of various sizes were prepared and weighed (Leinwage Type 1801 Sartorius Werke A/C). A magnetic material iron was chosen to ensure that the foreign bodies could be detected by a magnet if they became lost in the orbital tissue and could be easily removed when the investigation was complete. A total of 17 foreign bodies were used in the investigation five being placed intrachoroidally, eight intrasclerally and four retrosclerally. Enucleation was carried out either with a retrobulbar anaesthetic or under full anaesthesia. The conjunctiva was loosened in the usual manner along the limbus corneae and prepared as a flap the foreign body being placed

Localization of foreign body		
Intrachoroidal	Intrascleral	Retroscleral
1 - 4	5 - 9	10 - 12

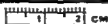


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Table 1
Weight of foreign body (iron) in mg

No	Intra choroidal weight	No	Interscleral weight	No	Retroscleral weight
1	0.051	5	0.190	10	0.787
2	0.577	6	0.374	11	0.768
3	0.153	7	1.159	12	1.456
4	0.316	8	0.635		
		9	0.310		

transducer until the echogram reflected the body in the form of a high peak. After the detection of the foreign body had been established its topographic location in relation to the scleral wall was determined by increasing the sensitivity to 40–50 db. This gave echograms showing the posterior bulbar wall, the foreign body and the orbital structure. The photographic registration was made with a Polaroid Oscilloscope camera System Kretztechnik and Land Film Type 107. All foreign bodies (17) could be identified in this manner and localized in relation to the posterior scleral wall. Some of the foreign bodies were of almost equal size and gave almost identical ultrasonograms. For this reason one intrachoroidal, three intrascleral and one retroscleral foreign body were excluded from further discussion. Fig. 1 shows those foreign bodies which remained (No. 1–12) and Table I gives their weights. In the following the ultrasonograms of the foreign bodies are numbered in accordance with the numbers given in Fig. 1 and Table I.

Results

Foreign body No. 1 situated in the choroid was the smallest foreign body examined (Fig. 1, Table I). It weighed 0.081 mg and measured approx. 0.5×0.4 mm. Figs. 2 A, B and C show how this foreign body was located echographically at a low (30 db) sensitivity level. The echographic findings when the ultrasound beam missed the foreign body are shown in Figs. 2 A and B (transducer position T_1 and T_2) in Fig. 2 C when the beam is focused on the foreign body (1) (transducer position T_3). When the apparatus was set at a low sensitivity level 30 db the biological structures in the posterior bulbar wall (retina, choroid, sclera) gave small, structurally undefinable echoes (Figs. 2 A and B). A foreign body of this magnitude (No. 1) was therefore reflected echographically in the form of a clearly higher echo (Fig. 2 C). Not until the sensitivity was increased to 40 db, however, could the topographic location of the foreign body in relation to structures in the posterior wall be ascertained (Fig. 2 D). The other intrachoroidal foreign bodies, Nos. 2–4 (Fig. 1, Table I) were of the magnitude 0.153–0.527 mg. The ultrasonograms of these foreign bodies are shown in Fig. 3.

The intrascleral foreign bodies were of the magnitude 0.120–1.159 mg and could all be diagnosed as being situated intrasclerally. The echograms of these foreign bodies, Nos. 5–9, are shown in Fig. 4.

Fig. 5 shows the ultrasonograms of the retroscleral foreign bodies, Nos. 10–12. As shown in Table I the weight of these foreign bodies was between 0.768 and 1.456 mg.

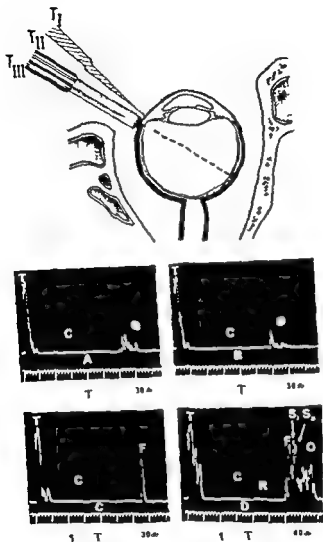


Fig 2

Detection (A B C) and topographic localization (D) of an intrachoroidal foreign body (No 1) (A) and (B) The ultrasound beam passing outside the foreign body (transducer position T₁ and T₂) (C) The beam is focused on the foreign body (transducer position T₃) (D) Higher setting (40 db) and tilting of the transducer permits visualization of retina foreign body and sclera T = transmitter pulse C = vitreous O = orbital tissue F = foreign body R = retina S₁ = anterior scleral wall S₂ = posterior scleral wall

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Results

Foreign body No. 1 situated in the choroid was the smallest foreign body examined (Fig. 1, Table I). It weighed 0.081 mg and measured approx. 0.5×0.4 mm. Figs. 2 A, B and C show how this foreign body was located echographically at a low (30 db) sensitivity level. The echographic findings when the ultrasound beam missed the foreign body are shown in Figs. 2 A and B (transducer position T_1 and T_2) in Fig. 2 C when the beam is focused on the foreign body (F) (transducer position T_3). When the apparatus was set at a low sensitivity level 30 db the biological structures in the posterior bulbar wall (retina, choroid, sclera) gave small, structurally undefinable echoes (Figs. 2 A and B). A foreign body of this magnitude (No. 1) was therefore reflected echographically in the form of a clearly higher echo (Fig. 2 C). Not until the sensitivity was increased to 40 db, however, could the topographic location of the foreign body in relation to structures in the posterior wall be ascertained (Fig. 2 D). The other intrachoroidal foreign bodies Nos. 2–4 (Fig. 1, Table I) were of the magnitude 0.153–0.327 mg. The ultrasonograms of these foreign bodies are shown in Fig. 3.

The intrascleral foreign bodies were of the magnitude 0.120–1.159 mg and could all be diagnosed as being situated intrasclerally. The echograms of these foreign bodies Nos. 5–9 are shown in Fig. 4.

Fig. 5 shows the ultrasonograms of the retroscleral foreign bodies Nos. 10–12. As shown in Table I the weight of these foreign bodies was between 0.165 and 1.456 mg.

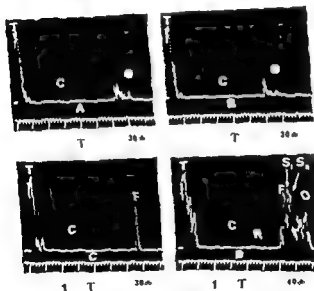
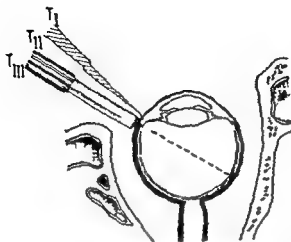


Fig 9

Detection (A B C) and topographic localization (D) of an intrachoroidal foreign body (Fig 1) (A) and (B) The ultrasound beam passing outside the foreign body (transducer position T and T₂) (C) The beam is focused on the foreign body (transducer position T₃) (D) Higher setting (40 db) and tilting of the transducer permits visualization of retina foreign body and sclera T = transmitter pulse C = vitreous O = orbital tissue F = foreign body R = retina S₁ = anterior scleral wall S₂ = posterior scleral wall

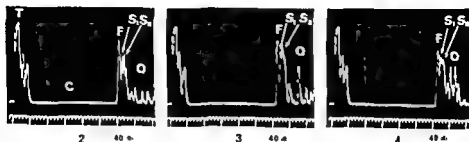


Fig 3

Ultrasonograms of the intrachoroidal foreign bodies Nos 2-4 T = transmitter pulse C = vitreous F = foreign body S_1 = anterior scleral wall S_2 = posterior scleral wall O = orbital tissue

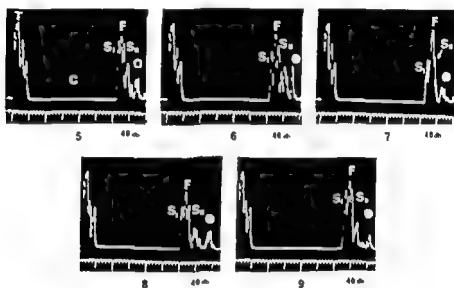


Fig 4

Ultrasonograms showing the intrascleral foreign bodies T = transmitter pulse C = vitreous S_1 = anterior scleral wall F = foreign body S_2 = posterior scleral wall O = orbital tissue

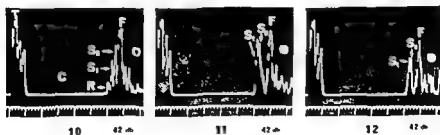


Fig 5

Ultrasonograms of the retroscleral foreign bodies T = transmitter pulse C = vitreous R = retina S_1 = anterior scleral wall S_2 = posterior scleral wall F = foreign body O = orbital tissue

DISCUSSION

Of the ocular structures in the retinal choroidal scleral complex the sclera is known to give the strongest echo reflections. Foreign bodies of a certain magnitude however will give a greater echo amplitude than these biological structures. With the same transducer and ultrasonograph as those used in this investigation the sclera examined *in vivo* gave an optimal amplitude of 1 cm at a sensitivity level of 30 db. An almost identical echo amplitude could be obtained from a plane piece of iron foil 0.2×0.2 mm whereas the echo from a similar piece of foil 0.25×0.25 mm was considerably higher than that from the sclera. Theoretically it should thus be possible to locate a foreign body of this reflection magnitude if it were situated in the sclera or foreign bodies of lesser reflection magnitude if situated in the retina or choroid. However it is not possible to fix an absolute limit for the size of a foreign body that can be identified echographically in the posterior bulbar wall as the reflecting echo depends to a certain degree on the shape (reflecting surface) of the foreign body. It was thus found that a steel ball with a diameter of 0.9 mm and a plane piece of iron foil 0.3×0.3 mm gave almost identical echo amplitudes. Usually however foreign bodies are polygonal in shape like those used in this investigation. Such foreign bodies rarely give such high echoes as corresponding foreign bodies with a plane reflecting surface but will give considerably higher amplitudes than spherical bodies. In this investigation the smallest intrachoroidal foreign body measured approx. 0.5×0.4 mm (0.031 mg) the smallest intrascleral body approx. 0.8×0.5 mm (0.120 mg) (Nos. 1 and 5 Fig. 1 Table I). Foreign bodies of this magnitude and with this location could be pinpointed and their topographic location determined in relation to the sclera. However this was possible only because the sensitivity level of the apparatus was kept so low (30–40 db) that echoes from the foreign body did not blend with echoes from the various biological structures in the posterior bulbar wall. On the other hand ultrasonic detection of the *retroscleral* foreign bodies was considerably more difficult. This was first and foremost because the boundary layer between scleral and orbital tissue gave such a high echo in certain positions of the transducer that they eclipsed even the echoes from the largest foreign bodies (Nos. III and 19 Fig. 1 Table I). It was therefore necessary to check the diagnosis of these foreign bodies by localization from several directions to eliminate any risk of a false foreign body echo. In contrast to foreign bodies located in the retinal choroidal scleral complex a *retroscleral* foreign body of ordinary size will never give a specific foreign body echo. This means that the ultrasonic diagnosis of foreign bodies in this location will be more complicated than in the case of intraocular or intrascleral bodies.

Ultrasonograph would appear to be capable of giving valuable information on the location of foreign bodies in relation to the biological structures in the posterior wall of the eye. In particular the method would seem to be a useful supplement to X-ray examination in cases where injury with double perforation is suspected and where the media are turbid in order to ascertain whether or not foreign bodies that appear on the X-ray are located intracocularly. In such circumstances ultrasonography will be the only method capable of establishing the presence and position of a non radio opaque foreign body.

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ON THE POSSIBILITIES OF ULTRASONIC DETECTION OF INTRAORBITAL FOREIGN BODIES

BY

JON S. LARSEN

Human orbital fat tissue removed at autopsy was used for ultrasonic examinations of standardized foreign bodies. The effect of attenuation of the ultrasound echo caused by orbital fat tissue was investigated. The foreign bodies quickly lost their echographical identity as they were covered by thicker layers of orbital fat. The limit for ultrasonic detection of foreign bodies with a reflecting echo corresponding to that of pieces of iron foil measuring 0.5×0.5 mm and 1.0×1.0 mm had been reached when they were buried beneath layers of orbital fat 1 mm and 3 mm thick respectively. Ultrasonography thus appears to be of use only in the detection of foreign bodies located in the superficial layers of the orbital fat. In clinical ophthalmology however it is important to be able to ascertain that foreign bodies in just this position are in fact located extrabulbally.

Key words: ultrasound - intraorbital foreign bodies

Ultrasonography has proved to be a valuable supplement to clinical and X-ray examination for the detection of intraocular foreign bodies including those not revealed by X-ray examination (Oksala 1959, 1960, Penner & Pasmore 1966, Punyan & Penner 1969, Coleman & Trokel 1971, Cowden & Runyan 1971).

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A scan ultrasound registration is also a suitable technique for localization of ocular foreign bodies in relation to the posterior bulbar wall. This method used alone or in combination with radiological methods is therefore found to be valuable for demonstrating or excluding double perforation (Gernet & Hennig 1966, Ossining & Scher 1969, Coleman & Trokel 1971).

Ultrasonic localization is best suited for intravitreal and other intraocular foreign bodies. In clinical ophthalmology as well as in experimental investigations foreign bodies may also be detected in extraocular orbital tissue (Ossining & Scher 1969, Larsen & Cjeruldsen 1973). The ophthalmic literature however does not give essential information on the ultrasonic findings to be expected of intraorbital foreign bodies.

The object of this work was to investigate further the echographical findings for foreign bodies located in orbital fat. The investigation was designed especially to ascertain to what degree the attenuation of ultrasound in orbital fat affects the possibility of ultrasonically detecting foreign bodies at this location.

Material and Methods

The apparatus used in the investigation was the Kretztechnik ultrasonograph model 7200 MA with an 8 MHz/5 mm plane transducer (NM 5 - 5 k). Normal human eyes obtained at autopsy on the first day post mortem were used in the examination. The eyes were removed together with the orbital fat. The material was placed in a moist chamber and the investigation begun within 2 hours at a temperature between 20 and 22°C.

The echo amplitude from foreign bodies depends largely on the size of the reflecting surface (Vanysek, Preisoví & Obráz 1970). In order to achieve as constant a reflecting surface as possible even without the guidance of sight three small steel balls were used as foreign bodies, their dimensions being 0.6 (K₁), 0.8 (K₂) and 1.0 (K₃) mm respectively. A quadrangular foreign body of iron foil (I₁) measuring 1.0×1.0×0.25 mm was also used. The investigation was carried out as follows:

- Five eyes were prepared so that only the posterior segment without retina and choroid was left. This was placed in a glass cylinder. The foreign bodies K₁, K₂, K₃ and I₁ were placed in turn on each of the scleral segments. The cylinder was filled with saline solution and the optimum echo amplitude was obtained from the bodies with the transducer on a stand placed perpendicularly over the foreign body/sclera. The optimal echo from the sclera with

out foreign bodies was also registered in all eyes. The distance from the transducer to the bottom of the sclera was always kept at 25 mm. During the examination the transducer was tilted until an optimum echo amplitude was obtained with the equipment set at sensitivity levels of 30, 36 and 40 db. At these sensitivity levels the optimal echoes from the sclera h_1 , h_2 , h_3 and F_1 were photographically registered with a Polaroid Oscilloscope Camera System (Kretztechnik and Land Film Type 10). Five registrations of amplitude were thus made from each object at each level of sensitivity. Subsequently a number of small quadrangular foreign bodies of various sizes prepared from plane iron foil 0.25 mm thick were examined in the same way. The purpose was to compare the echo amplitudes from these with those from h_1 , h_2 and h_3 .

Six preparations consisting of the posterior scleral segment with adjacent orbital fat in which the layer of fat adhering to the posterior pole was at least 10 mm thick, were used to determine the optimal echo from orbital fat. The preparation was placed in a glass cylinder with the scleral segment upmost. A metal ring was placed over the peripheral part of the preparation to hold it in position after the cylinder had been filled with saline water. The distance between the transducer and the sclera was also kept at 25 mm in this investigation. On tilting the transducer the highest echo amplitude found behind the sclera/orbital boundary was photographically registered as the maximal echo from the orbital fat. The maximal echo from the boundary layer between the sclera and orbital tissue was similarly registered. Registration was carried out at sensitivity levels of 30, 36, 40, 42 and 44 db.

To determine whether the sclera had any attenuating effect on the echo amplitude from a foreign body in all six preparations h_3 was placed between

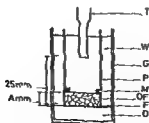


Fig 1

Schematic diagram of arrangement and measuring principle of reflectivity from foreign bodies under orbital fat. See text for further explanation.

the sclera and the orbital fat and the preparation positioned exactly as before with the transducer perpendicular above K_1 . After the optimal amplitude from K_1 had been obtained the sensitivity of the equipment was adjusted until the echo had the same amplitude as when K_1 was located on the sclera (series 1) at 30, 36 and 40 db and the db level was recorded.

3. The echographical measurements for K , K_1 and F_1 in orbital fat were made as shown in Fig. 1. A layer of orbital fat (O) was placed in a glass cylinder (C) and the foreign body ($I = K, K_1$ and F_1) was placed in the centre of the layer of fat (O). A layer of orbital fat (OI) 1–10 mm thick was placed in a transparent plastic tube (P) with millimeter scale. The plastic tube was then placed over the foreign body (I). A metal ring (M) which could be moved freely in the tube kept the fat in position when this and the glass cylinder were filled with saline water (W). The transducer (T) was kept attached to a holder placed perpendicularly over the foreign body (I). The optimal echo of the foreign body was then recorded photographically at sensitivity levels of 30, 36, 40, 42 and 44 db. Amplitude registrations were made with the transducer at a distance of 25 and $25 \pm \Delta$ mm from the foreign body. A representing the thickness of the fat layer that covered the foreign body.

Results

Fig. 2 shows a graphic survey of the optimal echo amplitudes obtained from the sclera (S), the boundary sclera/orbital tissue (SO) and orbital fat (O) and for foreign bodies K_1 , K , K_1 and F_1 . The amplitude given by K_1 was between that given by a piece of iron foil $0.2 > 0.2$ mm and one $0.25 > 0.25$ mm. The amplitude of K was almost identical with that from a piece of foil 0.9×0.9 mm and the amplitude of K_1 was almost equal to that from a piece of foil 0.95×0.95 mm. Uniform optimal echo amplitudes were obtained in the various measurements for all foreign bodies. No significant difference in echo amplitude could be measured whether the transducer was placed 25 or $25 \pm \Delta$ mm from the foreign body (Fig. 1). In contrast to the foreign bodies the biological structures showed individual differences in optimal echo amplitude approx. 2 mm for the sclera and approx. 4 mm for the boundary layer sclera/orbital tissue and for orbital fat. In the following the maximal echo amplitude registered for orbital fat is used.

When the echo amplitudes of K_1 measured with saline solution as medium were compared with those obtained when the ball was also covered by the

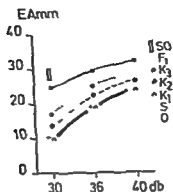


Fig 2

The optimal echo amplitudes (EA) obtained from orbital fat O the sclera S the boundary sclera/orbital tissue SO and from K₁ K₂ and F₁ with a saline medium. The abscissa gives the equipment sensitivity (db). K₁ K₂ and K₃ = steel balls with diameter of 0.6 0.8 and 1.0 mm. F₁ = iron foil 1.0 × 1.0 mm.

sclera, only a very moderate reduction of amplitude was found in the latter case. Compensation for the reduction could be achieved by an increase of 0.5 to 1.5 db. In other words, the attenuating effect of the sclera on the echo amplitude of the foreign body was so slight that the relation between the values found for foreign bodies and orbital fat (Fig 2) is not affected.

Fig 3 gives a graphic representation of the optimal echo amplitude of iron foil F₁ under layers of orbital fat with a thickness of 3, 4, 5 mm and 1–10 mm respectively. The maximal amplitude curve found for orbital fat (O) is also shown. (The highest echo amplitude obtained from orbital fat is considered as maximal amplitude.) The relation between the two curves is an expression of whether or not the difference in amplitude between F₁ and the surrounding fatty tissue would permit the foreign body to be detected echographically. From the figure it appears that the echo amplitude of F₁ was higher than that from orbital fat when the thickness of the fat layer was 3 mm (Fig 3A) whereas the maximal amplitudes from the fat and the foil (F₁) most closely approached equality when F₁ was covered by 4–6 mm orbital fat (Figs 3B and C). When F₁ was covered by more than 6 mm orbital fat (Figs 3D and E) the maximal amplitudes of the orbital fat were markedly higher than those from the foil (F₁). Fig 4 shows ultrasonograms illustrating the optimal echo amplitude obtained from F₁ with saline solution as medium (Fig 4A) at an equipment sensitivity level of 30 db when F₁ was covered by a 7 mm thick

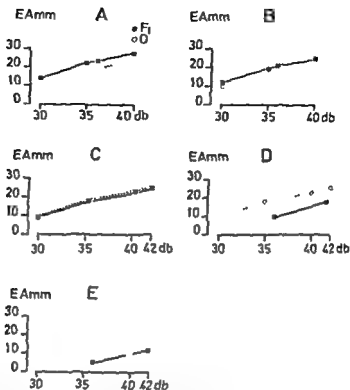


Fig 3

The optimal echo amplitude (EA) registered from orbital fat O and from F₁ covered by orbital fat. The abscissa gives the equipment sensitivity (db). F₁ is buried beneath 3 mm orbital fat in A, beneath 4 mm in B, beneath 5 mm in C, beneath 6 mm in D, and beneath 7-10 mm in E.

layer of orbital fat (Fig 4 B). As shown by Fig 4 A and B, there was a marked reduction in amplitude from F₁ when it was covered by a 7 mm thick layer of fatty tissue. Even when the equipment sensitivity was increased from 30 (Fig 4 B) to 42 db (Fig 4 C), the amplitude from F₁ registered through a 7 mm thick layer of fat was still less than that obtained with a saline medium at 30 db (Fig 4 A). Figs 4 B and C show only the optimal echo amplitude from F₁; the maximal amplitude obtainable from the fatty tissue, which is used in the curves shown in Figs 3 and 5, has not been included.

Fig 5 is a graphic presentation of the corresponding findings for K₁ situated beneath a 1-5 mm thick layer of orbital fat. As shown, K₁ gave a higher echo than the maximal amplitude of the orbital fat when the ball (K₂) lay beneath a 1 mm thick layer of fat (Fig 5 A). On the other hand, if the ball lay beneath a 3 mm thick layer of fat (Fig 5 B) or beneath a layer of 4 or 5 mm respectively (Figs 5 C and D), the optimal echo of the orbital fat exceeded that of the ball to an increasing degree.

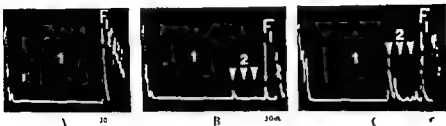


Fig 4

The echogram in A shows the optimal echo amplitude obtained from F_1 with a saline medium at equipment sensitivity of 30 db. The echograms in B and C show the considerable reduction in amplitude which occurred when F_1 was buried beneath a layer of orbital fat 7 mm thick. B indicates the amplitude at an equipment sensitivity level of 30 db. C at 47 db. 1 = saline solution 2 = orbital fat.

Similar investigations were carried out for K_2 with the ball situated beneath a 1 mm thick layer of orbital fat. The echo amplitude found for K_2 was however so reduced that it was markedly exceeded by the maximal amplitude from the orbital fat. It was therefore not possible to detect the ball echographically on the basis of the height of the echo.

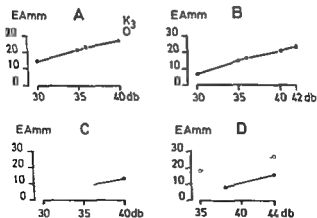


Fig 5

The optimal echo amplitude from orbital fat (O) and from the ball K_2 covered by orbital fat K_3 = buried beneath 1 mm orbital fat in A, beneath 3 mm in B, 4 mm in C and 5 mm in D.

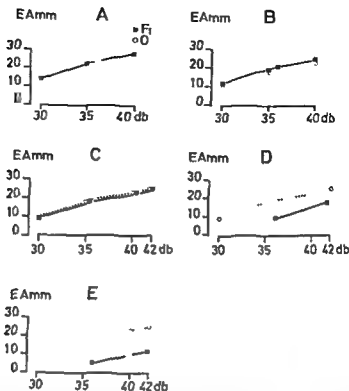


Fig 3

The optimal echo amplitude (EA) registered from orbital fat O and from F_1 covered by orbital fat. The abscissa gives the equipment sensitivity (db). F_1 is buried beneath 3 mm orbital fat in A, beneath 4 mm in B, beneath 5 mm in C, beneath 6 mm in D, and beneath 7–10 mm in E.

layer of orbital fat (Fig 4 B). As shown by Fig 4 A and B, there was a marked reduction in amplitude from I_1 when it was covered by a 7 mm thick layer of fatty tissue. Even when the equipment sensitivity was increased from 30 (Fig 4 B) to 42 db (Fig 4 C), the amplitude from F_1 registered through a 7 mm thick layer of fat was still less than that obtained with a saline medium at 30 db (Fig 4 A). Figs 4 B and C show only the optimal echo amplitude from I_1 ; the maximal amplitude obtainable from the fatty tissue which is used in the curves shown in Figs 3 and 5 has not been included.

Fig 5 is a graphic presentation of the corresponding findings for K_3 situated beneath a 1–5 mm thick layer of orbital fat. As shown, K_3 gave a higher echo than the maximal amplitude of the orbital fat when the ball (K_3) lay beneath a 1 mm thick layer of fat (Fig 5 A). On the other hand, if the ball lay beneath a 3 mm thick layer of fat (Fig 5 B) or beneath a layer of 4 or 5 mm respectively (Figs 5 C and D), the optimal echo of the orbital fat exceeded that of the ball to an increasing degree.

ordinary size will therefore not give a specific amplitude. In *in vivo* examinations it would therefore seem necessary to pinpoint a foreign body in the orbit from various directions in order to ensure a correct ultrasonic diagnosis.

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As shown by Fig 2 the optimal echo amplitudes for the sclera orbital fat and the smallest steel ball (k_1 - diameter 0.6 mm) were found to be almost identical k_1 was therefore not reflective enough to permit its identification by ultrasonography on the basis of the height of its echo when it was situated under the sclera or orbital fat

Discussion

Ultrasonic detection of foreign bodies in the orbit appears to be limited by the following two factors

- 1 The attenuation of ultrasound in orbital fat which is an absolute limit and
- 2 The strong echo reflections of the biological structures in the orbital tissue which complicate the echographical findings to such a degree that they set a relative limit to echographical detection

The study showed that it was the size (reflecting surface) of the foreign body and the thickness of the layer of fat in which it was buried that determined whether or not it could be identified by ultrasonography (Figs 3 and 5) The findings made with k_3 demonstrate that a foreign body with a reflecting capacity corresponding to that of a piece of iron foil 0.35×0.35 mm could be identified echographically when buried under a layer of fat 1 mm thick The limit for echographical detection of a foreign body 1.0×1.0 mm (k_1) had been reached when it was buried beneath a layer of fat approx 3 mm thick These findings represent the maximal limits for ultrasonographical identification of foreign bodies buried in orbital fat The requirement for identification was that the foreign body should be reflected on the echogram with a markedly higher amplitude than the surrounding fatty tissue The findings thus showed that foreign bodies quickly lose their echographic identity on penetration into orbital fat

Orbital fatty tissue lacks ultrasonographic homogeneity and the tissue itself gives high reflecting echoes If the equipment is set at a high sensitivity level the result will be that the foreign body echo will merge with the echo from the orbital tissue and will not be identifiable An intraorbital foreign body will therefore only be reproduced visibly in the echogram if the equipment is set at a low sensitivity level (30-40 db's MHz transducer) The boundary layer between the sclera and orbital fat may however have a greater reflective capacity than even large foreign bodies if the transducer is in a position that gives optimal reflection (Fig 2) Retrobulbar foreign bodies of

ordinary size will therefore not give a specific amplitude. In *in vivo* examinations it would therefore seem necessary to pinpoint a foreign body in the orbit from various directions in order to ensure a correct ultrasonic diagnosis.

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**PEROXIDASE DIFFUSION
IN THE RABBIT CILIARY BODY IN
EXPERIMENTAL UVEITIS**

A light microscopic study

BY

OLAV ØYVIND PEDERSEN

Experimental uveitis has been produced in albino rabbits by injection of human serum albumin into the vitreous body. To study the blood aqueous barrier in the ciliary body in experimental uveitis horseradish peroxidase has been used as a cytochemical tracer by light microscopy.

After intravenous injection of peroxidase it gained ready access to the posterior chamber in the uveitis eyes. The diffusion barrier to peroxidase in the ciliary epithelium was broken in localized areas. At these sites heavy infiltration of leukocytes was found and a continuous epithelial lining was apparently lacking. Outside these areas the diffusion barrier to peroxidase was found intact.

Key words: experimental uveitis - blood aqueous barrier - peroxidase diffusion - light microscopy - ciliary body - rabbit

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1969) Interest has been focused mainly on the cellular reactions. The pathophysiological mechanisms of the breakdown of the blood aqueous barrier is poorly understood. Tracer experiments might give additional information concerning this problem.

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The purpose of the present investigation was to study the blood aqueous barrier to horseradish peroxidase in the rabbit ciliary body in experimental uveitis by means of light microscopy.

Material and Methods

Nine healthy adult albino rabbits weighing 2.5–5 kg were used. Before experimentation all eyes were determined to be normal by slit lamp and ophthalmoscopic examination. Uveitis was produced in the left eyes of eight animals by intravitreal injection of 0.1 ml of a solution of human serum albumin. 0.1 ml sterile Ringer solution was injected into the right eyes of these animals. The eyes of one animal were not injected at all.

The albumin solution was prepared by dissolving 100 mg crystalline human serum albumin (AB Labi, Stockholm) in 1 ml Ringer solution. The solution was sterilized through a Millipore filter (pore size 0.2 μ m) immediately before use.

After topical anesthesia with 0.2% oxibuprocaine the solution was injected slowly into the vitreous body about 2 mm anterior to the equator. Care was taken to avoid damaging the ciliary body and the lens capsule.

In the antigen-treated eyes anterior uveitis developed about a week later. At the time of enucleation 1 to 6 days after onset of the uveitis the eyes showed pericorneal injection. Aqueous flare, cells and fibrin were observed in the anterior chamber. Marked iris hyperemia was found. Frequently posterior synechiae were present but there was no sign of seclusion or occlusion of pupillae in any of the eyes. The lenses appeared normal. Moderate blurring of the vitreous body occurred. The control eyes showed no sign of inflammation.

Eight animals were injected intravenously with 250–500 mg commercial horseradish peroxidase (Sigma type II) dissolved in 5 ml sterile Ringer solution. One, 2, 5, 10, 15 and 30 mm after the peroxidase injection the animals

*University Eye Department
(Head Prof Thore Lie Thomassen)
Rikshospitalet Oslo Norway*

**PEROXIDASE DIFFUSION
IN THE RABBIT CILIARY BODY IN
EXPERIMENTAL UVEITIS**

A light microscopic study

BY

OLAV ØYVIND PEDERSEN

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Fig 1

Peroxidase distribution in the ciliary body of a control eye that was enucleated 2 min after intravenous injection of peroxidase. Peroxidase reaction product is present in the blood vessels (bv), the stroma (s) between the basal epithelial cells (be) and in the intercellular space (arrows) between the basal and the superficial epithelial cells (se). No reaction product is seen between the superficial epithelial cells. Posterior chamber (pc). Unstained section $\times 100$.

were decapitated and both eyes were enucleated immediately. The eyes were opened at the equator and immersed in ice-cooled fixative.

For perfixation 1% and 2.5% glutaraldehyde in 0.1 M phosphate buffer pH 7.4 were used. To the 1% solution 4% sucrose was added. After fixation for about 10 min the eyes were divided into two parts at the equator and the lenses were removed from behind. Broad sectors (3–4 mm) were taken from the ciliary bodies and the fixation was continued for 1 to 3 hours. The tissues were washed overnight in cooled 0.1 M phosphate buffer pH 7.4 containing 5% sucrose. The blocks were then cut into pieces of 0.5–1 mm in thickness and in some instances sclera was gently removed. The pieces were washed briefly in cooled distilled water and incubated for 15–30 min at room

temperature in tris HCl buffered diaminobenzidine H₂O solution pH 7.6 (Karnovsky 1961). In some instances sections 40 μ m thick cut on a CO₂ equipped freezing microtome were incubated. The tissues were washed for 10 min in three changes of cooled distilled water postfixed in 1% OsO₄ in Millonig's phosphate buffer pH 7.4 dehydrated in ethyl alcohol treated with propylene oxide and embedded in Epon 812.

Semi thin sections were examined either unstained or stained with toluidine blue.

As cytochemical control one rabbit suffering from uveitis was injected intravenously with 5 ml sterile Ringer solution without peroxidase and tissues were fixed and processed as for cytochemical reactions.

As substrate controls tissues from peroxidase injected rabbits were incubated in media without either H₂O₂ or the diaminobenzidine.

The Ringer injected eyes served as uveitis controls as well as both eyes from the rabbit whose eyes had not been injected.

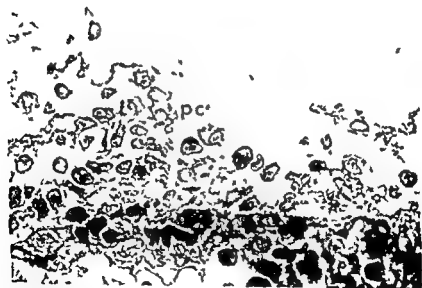


Fig. 2

Break in the epithelial diffusion barrier to peroxidase in the ciliary body of a uveitis eye. Peroxidase reaction product is seen in the ciliary stroma (s) and the posterior chamber (pc). Note disintegration of the epithelial lining and heavy cellular infiltration. The eye was enucleated 1 min after peroxidase injection. Toluidine blue $\times 750$.

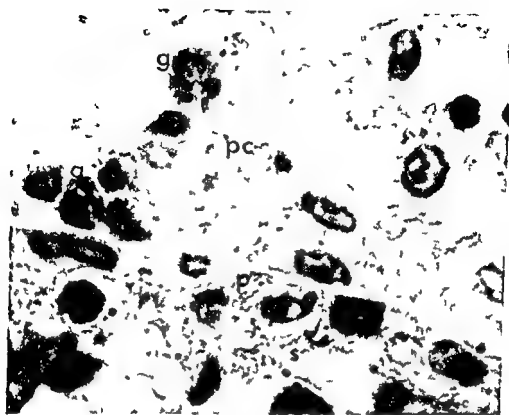


Fig 9

Detail from area where the epithelial diffusion barrier to peroxidase is broken. Peroxidase reaction product (p) can be followed continuously from the ciliary stroma (s) to the posterior chamber (pc). Note apparent absence of a continuous epithelial lining. Granulocytes (g). Toluidine blue $\times 1830$.

Results

All sections from peroxidase injected animals showed a dark brown peroxidase reaction product if the tissue had been incubated in the complete medium. Sections from tissue incubated *in bloc* showed reaction product only at the periphery of the blocks. When glutaraldehyde fixed frozen sections were incubated in the complete medium the stroma of the ciliary body was stained all through. *In bloc* incubation however proved satisfactory for investigation of the epithelial diffusion barrier and was the method generally employed in the present work.

Sections of tissues taken from the animal not injected with peroxidase showed endogenous peroxidase activity in erythrocytes and leukocytes when these tissues had been incubated in the complete medium. No reaction product was

seen in sections taken from tissues incubated in media which omitted either H_2O or the diaminobenzidine (Fig 5)

Regarding the nomenclature of the epithelial cell layers of the ciliary body in the following the terms basal and superficial are used as pertaining to the stroma and to the posterior chamber respectively

Ultrastructural studies of normal eyes from mice and monkeys using peroxidase as a tracer have shown that the capillaries of the ciliary body are permeable to this tracer and that the blood aqueous barrier in the ciliary body to this protein is located basally in the superficial epithelial cell layer (Shiose 1970 Smith 1971 Vegge 1971 a) Diffusion of peroxidase injected intravenously is halted by zonula occludentes girdling the basis of the superficial epithelial cells Fig 1 presents peroxidase distribution in the ciliary body of a control eye that was enucleated 2 min after injection of the tracer Reaction product is seen in the blood vessels the stroma between the basal epithelial cells and in the intercellular space between the basal and the super

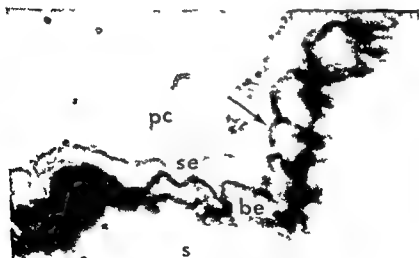


Fig 1

From a ciliary process of a uveitic eye The epithelial diffusion barrier to peroxidase is intact in this area Peroxidase reaction product is seen between the superficial (se) and the basal (be) epithelial cell layer (arrow) but not in the intercellular spaces between the superficial epithelial cells Posterior chamber (pc) Stroma (s) Unstained section $\times 1830$

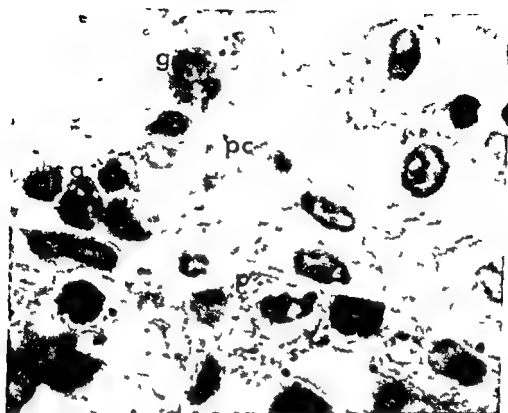


Fig. 3

Detail from area where the epithelial diffusion barrier to peroxidase is broken. Peroxidase reaction product (p) can be followed continuously from the ciliary stroma (s) to the posterior chamber (pc). Note apparent absence of a continuous epithelial lining. Granulocytes (g). Toluidine blue. $\times 1830$.

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Discussion

The present study indicates that the epithelial diffusion barrier to peroxidase and probably also to the serum proteins is intact in large parts of the ciliary body in experimental uveitis of the present type and severity. However, in localized areas the epithelial barrier is destroyed and peroxidase gains access to the posterior chamber. These breaks in the barrier may represent sites of serum protein leakage as well. Bill (1964-68) using isotopically labeled albumin and gammaglobulin has shown that these substances permeate the ciliary vessels under physiological conditions. Moreover, during a severe inflammation of the uveal tract the vascular permeability of the ciliary vessels to isotopically labelled albumin and gammaglobulin is greatly enhanced (Gamble, Aronson & Brescia 1970; Aronson et al. 1971). Accordingly, considerable amounts of serum proteins gain access to the ciliary stroma both under physiological conditions and during acute anterior uveitis. The gross pathological changes at the sites of peroxidase leakage, including apparent lack of a continuous epithelial lining, support the assumption that serum proteins here can enter the aqueous humor, even though peroxidase has a smaller molecular weight than the serum proteins. Horseradish peroxidase (Sigma type II) has a molecular weight of about 40 000 (Klapper & Hackett 1965). The molecular weight of active units is not altered by injection of the tracer into the blood stream (Vegge, Winther & Olsen 1971).

Wegner (1961) has studied effects of anesthetics on the structure of the rabbit ciliary body and found that urethan and pentobarbital anesthesia provoked an edematous change of the anterior (iridial) processes and ultrastructural changes of the epithelium, while ciliary bodies obtained from non-anesthetized rabbits killed by decapitation or air embolism did not show these changes. Although these observations cannot be regarded as conclusive (Kozart 1968), they stress the necessity for careful handling and show that meticulous precautions have to be taken to avoid changing the physiological conditions when experimenting with rabbit eyes. On the basis of these observations, in the present work the eyes were obtained after decapitation. Edematous changes of iridial or ciliary processes were not observed in any of the eyes that had not received antigen.

Commercial horseradish peroxidase can itself induce vascular leakage in certain species in association with degranulation of mast cells (Cotran & Karnovsky 1967). As the rabbit uvea contains mast cells, this might also be the case in this tissue. However, the localization of peroxidase in the rabbit ciliary body as seen in this study and by electron microscopy (Pedersen 1973) agrees with studies on mice (Shiose 1970; Smith 1971) which appear to be resistant



Fig 3

From the ciliary body of a uveitis eye of a peroxidase-injected animal. Section from tissue incubated in medium lacking H_2O_2 . Note absence of peroxidase reaction product. Unstained section. Phase contrast. $\lambda \sim 50$.

ficial epithelial cell layer. This distribution was seen in all eyes that had not received antigen and is in accordance with the ultrastructural studies mentioned above.

In the antigen treated eyes marked edema was observed in the iridial and ciliary processes. Cellular infiltration predominantly monomorphonuclear cells was present. The cellular infiltration was patchy. In some areas it was moderate while in others heavy infiltration of cells occurred. In the eye enucleated as early as 1 min after peroxidase was injected the tracer was found in the posterior chamber (Fig 2) showing that the blood aqueous barrier to this protein was broken. In localized areas peroxidase reaction product could be followed continuously from the stroma to the posterior chamber (Figs 2S) indicating that these foci represent sites of peroxidase leakage. In these areas heavy infiltration of monomorphonuclear cells was found and a continuous epithelial lining was apparently lacking (Fig 3). Now and then scattered granulocytes were seen. In other areas no reaction product was seen between the superficial epithelial cells indicating an intact diffusion barrier to peroxidase (Fig 4). Whether the eyes were enucleated early or late after the peroxidase injection made no appreciable difference to the localization of peroxidase.

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to this action of peroxidase. Moreover, by electron microscopy of normal rabbit iris vessels these were found to be impermeable to peroxidase (Pedersen 1973) as they are in mice (Smith 1971). These observations agree with studies on monkeys (Vegge 1971 a, b). Hence such effects of peroxidase do not seem to alter significantly the physiological conditions in the rabbit uvea.

Segawa & Smelser (1969) in their electron microscopic study of experimental uveitis found no alterations indicative of a breakdown of the blood aqueous barrier in the regions closely related to the monomorphonuclear cell response. However, small islands of polymorphonuclear heterophilic infiltration occurred and near them were found disruptions of both the desmosomal linkages and the internal limiting membrane of the ciliary epithelium. They suggest that these leukocytes rather than the monomorphonuclear leukocytes play an important direct role in the breakdown of the blood aqueous barrier. In the present work heavy infiltration of monomorphonuclear cells was found in areas associated with peroxidase leakage. Granulocytes were seen now and then but were not present constantly. Different lengths in the time interval between the onset of uveitis and the enucleation and the use of another antigenic stimulus may account for differences between the histopathological picture as seen by Segawa & Smelser (1969) and that observed in the present work. Thus in group II of Segawa & Smelser polymorphonuclear leukocytes were more prominent in the eyes enucleated 1 day after the onset of the uveitis compared with those enucleated after 7 days. The animals in this group were immunized by a single intravitreal injection of 10 mg bovine serum albumin. When eyes were treated with 40 mg of this antigen a more massive cellular infiltration was found and it consisted mainly of polymorphonuclear leukocytes.

On the basis of the observations in the present work only limited conclusions can be drawn concerning the pathophysiological mechanisms of the breakdown of the functional protein diffusion barrier. Breaks in this barrier were always associated with heavy cellular infiltration. This infiltration may play a direct role in the breakdown of the blood aqueous barrier but it may also be a secondary or accompanying phenomenon. This problem however remains to be solved and lends itself to further investigations.

This study is presently being followed up by electron microscopic studies on the same topic.

Acknowledgment

The author is indebted to Rolf Seljelid M.D. The Norwegian Radium Hospital, Oslo for valuable technical advice. Financial support from the Norwegian Research Council for Science and the Humanities is gratefully acknowledged.

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TRANSACTIONS OF
THE DANISH OPHTHALMOLOGICAL SOCIETY
1971-1972

BY

E GOLDSCHMIDT Secretary

439th Meeting Oct 2 1971 at Odense Hospital

J Edmund and N Rosenberg *The Postgraduate Training*

K Knudtzon and K Dressler *Postdiploma Education*

V Dreyer E Preisler and N Willumsen *Ophthalmological Specialist Practice in the 10's*

After a long and animated discussion a committee was appointed to submit recommendations for the future structure of specialist practice

*440th Meeting Held jointly with the Ophthalmological Society
of Southern Sweden on Oct 29 1971 at Rigshospitalet
Copenhagen*

B Bengtsson *Normal Ranges in Tonometry Acta ophthal (Kbh) 50 (1972)
33-47*

Discussion K Nørskov E Gregersen N Ehlers

H Bynke C E T Krakau and F Wilke *Repeated Tonometry in Optic Nerve Lesions*

At repeated tonometry the tension is usually found to be declining (Stocker Goldmann Bechrakis and others). In applanation tonometry every minute the reduction in tension amounts to 3-4 mmHg in 5 minutes. The cause of this effect is unknown. In an effort to elucidate the role of the nerve path in this effect eight patients with unilateral optic nerve lesion were subjected to repeated applanation tonometry. Measurement once a minute on the healthy eye showed a mean fall of 2.2 mmHg in 5 minutes. At the same time a consensual fall of tension of 1.3 mmHg occurred in the other eye. At repeated tonometry on the affected eye the fall of tension was 0.7 mmHg in

5 minutes and the consensual fall in the healthy eye 0.9 mmHg

In four patients with unilateral visual impairment down to light perception due to cataract a normal fall of tension was found in both eyes at repeated tonometry. In two patients with bilateral mydriasis induced by Cyclogyl and Neosynephrine 10% the same fall was observed.

The experiments indicate that the mechanism is related to that described by Ruse and Simonsen in their water drinking tests on patients with unilateral optic nerve atrophy.

Discussion S E Simonsen H Bynke

J A Fahmy Vitreous Haemorrhage in Subarachnoid Haemorrhage - Tersons Syndrome Acta ophthal (Kbh) 50 (1972) 131-143

A 66 year old man suffered bilateral vitreous haemorrhage in connection with a ruptured left sided carotid aneurysm. The less severe haemorrhage in the left vitreous cleared in 4 weeks without sequelae, the profuse right sided haemorrhage not until 1 month later. The patient was left with a permanent visual impairment in the right eye due to degenerative macular changes possibly due to the degradation products of haemoglobin (iron).

Vitreous haemorrhage must be considered a more common occurrence in subarachnoid haemorrhage than hitherto has been assumed.

Discussion H Bynke S Ry Andersen P Brøndstrup O J Jensen A Eilers

O Holm and C E T Krakau Measurement of Cupping of the Optic Disc

Cupping of the disc was measured by a photogrammetric method. A number of parallel slits are projected over the disc which is photographed with a fixed angle (15°) between the axes of the projector and camera. Each of the slits affords an optic section through the excavation. Planimetry of the surface closed in between the slit pictures over the bottom of the disc and a baseline determined by the disc edge was carried out for each slit after which the surfaces were summed up and afforded a direct measure of the disc volume. When the magnification factors and the distance between the slits are known this volume may be expressed in absolute figures.

The photography is done by a slit camera on which the slit is replaced by a grid of parallel lines and the microscope part is replaced by a one eyed mirror reflex camera. Goldmann's contact lens is used so that the degree of magnification within the system is largely independent of the patient's refraction. In repeated measurements the standard deviation was usually 5-10%.

The method has been employed in a material of some 200 patients with glaucoma suspected of glaucoma and normals by Becker and Holm in St Louis. In their material the difference in cupping between the right and left eye was most marked in the group with glaucoma. They also pointed out the importance of performing measurements on several occasions on the same patient.

Continued investigations using this method are predominated by questions of the type: Will the increase in excavation invariably lead to a visual field defect and if so can the development of a visual field defect be prevented by regulating the tension as soon as the cupping starts enlarging?

O A Jensen and J Kleener Clinical and Histopathological Study of Intraocular Pseudotumours in Children in Denmark 1941-1966 Acta ophthal (Kbh) 49 (1971) 902-912

A clinical and histopathological study of the intraocular pseudotumours enucleated in Denmark during the period 1919-1966. The material comprises 20 eyes from 45 children.

The findings were compared with those in a similar study by O. A. Jensen on Danish children with retinoblastoma.

Coats disease accounted for one third of the pseudotumours, inflammatory lesions for one third, and malformations plus other changes for one third. Coats disease was twice as common in boys as in girls and occurred mainly in children older than those who made up the retinoblastoma material.

There were three cases of congenital retinal dysplasia, all in girls under 1 year of age.

The amaurotic cat's eye was the most common sign in retinoblastomas as well as in the pseudotumours, but twice as common in retinoblastoma as in pseudotumours. Inflammatory eye and the too small eye found in 13% and 9% respectively of the pseudotumours did not occur in the Danish material with retinoblastoma. Microphthalmia militates against retinoblastoma. A bilateral occurrence was more common among the patients with retinoblastoma.

On the basis of the investigation the most common diagnostic criteria for pseudotumour and retinoblastoma were established.

Holm *An Optic Reading Device for the Blind*

A reading device for the blind, the Optacon (Optical to tactile converter), developed at Stanford University and Stanford Research Unit in Palo Alto, California, allows blind people to read ordinary print at 50-100 words per minute. The optical image of each letter is converted to a vibration pattern of exactly the same shape as the letter. The vibration pattern is perceived by the finger tip.

The Department of Experimental Ophthalmology at the University Eye Clinic in Lund has recently started pilot studies of the Optacon.

Discussion *H. Skjoldsgaard, S. F. Simonsen*

M. Norn *Defects in the Pigmented Layer of the Iris in Uveitis and in Normals*
Acta ophthalmol. (Aab.) 49 (1971) 887-894 and 895-901

Discussion *A. Dreisler* asked whether iris pigment defects in uveitis depended upon the treatment given.

Norn I have observed a case of pigment defects to arise at the first dilatation treatment of the initial attack of iritis. The development of the defects depends upon the number of previous attacks, the time when the dilatation treatment is started, the patient's age, etc. Of course dilatation of the pupil must not be omitted in iritis. This treatment is necessary to avoid secondary glaucoma.

O. A. Jensen asked whether the defects in the elderly patients of the material might be imagined to be due to repeated attacks of uveitis.

Norn In my opinion the defects in the elderly patients cannot be explained in this way because these patients have not exhibited signs of uveitis, acute glaucoma, trauma or other conditions which may give rise to pigment defects. No less than 72% of normal 50-year-old persons show juxtapupillary defects of the iris pigment. I interpret this as wear and tear caused by the physiological movements of the pupil.

441st Meeting Dec 4 1971 Rigshospitalet Copenhagen

The meeting was conducted by the ophthalmopathologists from the Ophthalmic Pathology Laboratory. About 20 cases were presented first by a report of each case history by the departments concerned thereafter by histopathological demonstrations including photomicrographs. An animated discussion followed.

442nd Meeting Feb 18 1972 Rigshospitalet Copenhagen

S. Ry Andersen: Fundus Changes in Hypertension Elucidated Clinically and Histopathologically

Keith Wagener and Barker's method of classifying hypertensive fundus changes was assessed on the basis of about 4000 personally performed ophthalmoscopic examinations at St. Lukas Hospital in Hellerup. These were supplemented by a number of routine histological studies of enucleated and autopsy eyes from the Ophthalmic Pathology Laboratory, Copenhagen.

During recent years I have clinically modified the method of classification trying to render it semiquantitative by a + ++ +++ graded assessment of changes in calibre crossing phenomena reflex changes generalized vascular constrictions venular changes haemorrhages exudates stellate figures papilloedema etc. The findings are entered on a form stamped in the case notes and the total changes are evaluated and classified into stages I II III III-IV and IV. All the cases are assessed individually paying due regard to age.

Among deviations from the classic grouping it may be mentioned that haemorrhages with vascular changes are placed in group II-III whereas cotton wool exudates always a serious sign are assigned to group III like really severe arteriolar changes including generalized severe vascular constriction. Severe vascular changes are listed as malignant.

It was discussed whether the time had come to omit the word hypertension entirely from the diagnosis as the ophthalmoscopic examination deals more with an evaluation of the condition of the vessels including the degree of arteriosclerosis and permeability. It was suggested to use the term retinal vascular lesion group I-IV possibly abbreviated RVL gr I-IV.

Discussion: T. Hilden, P. Brandstrup, P. M. Møller, H. Bynke, N. Ehlers, N. Th. Rosenberg, N. Willumsen, J. Giese

J. Hvidberg Hansen and F. Erlin Larsen: Congenital Cysts of the Iris. Acta ophthalmol. (Kbh.) 50 (1962) 501-514

Discussion: O. A. Jensen

A. Braun Larsen: Pyruvate and Citrate Concentrations in Bovine Aqueous Humour. Acta ophthalmol. (Kbh.) 50 (1972) 420-430

Discussion: O. A. Jensen

M Møller Treatment of Congenital Glaucoma

During the past 6 years an attempt has been made to centralize the treatment of congenital glaucoma in Odense. During this period 23 patients have been treated.

Submitted in particular the results of treating 25 eyes by Worst goniotomy.

All the patients were under 1 year of age. The follow up period was from 9 months to 11 years. Nineteen eyes are well controlled.

On the other hand it has not proved possible to control four eyes in patients with Lowe's syndrome and Rieger Axenfeld's iridocorneal dysgenesis by Worst goniotomy.

The operations were carried out by hydrostatic anterior chamber needle and Worst's special gonio lens with fibre light sutured to the sclera.

Discussion S Ry Andersen H Skydsgaard E Gregersen Sv Kessing O A Jensen G Pouplier E Goldschmidt

E Gregersen and S Kessing recommend the use of Harms trabeculotomy. They submitted their preliminary results and referred to Harms analysis showing 100% good results of this method.

P M Møller We realize that especially patients with Rieger Axenfeld's anomaly would do best when treated by trabeculotomy.

E Dreisler Colour Blindness and Choroideraemia

Discussion E Goldschmidt V Dreier H Skydsgaard

Erik Krogh Extracorporeal Ionizing Radiation of the Blood and Corneal Grafts

The possible role of cellular hypersensitivity in corneal graft rejection was discussed. Extracorporeal ionizing radiation of the blood, a specific suppressor of cellular hypersensitivity, has been employed in two patients undergoing corneal retransplantation. Results, conclusions and consequences were reported.

J Fahmy Papilloedema in Intracranial Aneurysms Acta ophthal (Kbh) 50 (1972) 93-807

Papilloedema occurs in 16% (99% confidence limits 10-24) of all cases of intracranial aneurysms. The papilloedema is slight and as a rule associated with retinal haemorrhage of varying degree. About one-fifth of the cases of papilloedema were unilateral and occurred in six out of seven cases on the side of the aneurysm or haematoma. No relationship was found between arterial hypertension, cerebral arteriosclerosis, intracerebral haematoma, arachnoid adhesion and the occurrence of papilloedema. An increased operative risk was demonstrated in patients having papilloedema.

M Norn Vital Staining with a Tetrazolium Alcian Blue Mixture

Vital staining with a tetrazolium alcian blue mixture is indicated in cases of conjunctival complaints. A punctate red staining on the superior or inferior tarsus supports the diagnosis of simple chronic conjunctivitis.

A predominantly green thread of mucus in the inferior fornix shows that the conjunctiva is sterile, whereas a predominantly red thread of mucus is seen in infectious bacterial conjunctivitis.

441st Meeting Dec 4 1971 Rigshospitalet Copenhagen

The meeting was conducted by the ophthalmopathologists from the Ophthalmic Pathology Laboratory. About 20 cases were presented first by a report of each case history by the departments concerned thereafter by histopathological demonstrations including photomicrographs. An animated discussion followed.

442nd Meeting Feb 18 1972, Rigshospitalet Copenhagen

Ry Andersen *Fundus Changes in Hypertension Elucidated Clinically and Histopathologically*

Keith Wagener and Barker's method of classifying hypertensive fundus changes was assessed on the basis of about 4000 personally performed ophthalmoscopic examinations at St. Lukas Hospital in Hellerup. These were supplemented by a number of routine histological studies of enucleated and autopsy eyes from the Ophthalmic Pathology Laboratory, Copenhagen.

During recent years I have clinically modified the method of classification trying to render it semiquantitative by a + ++ +++ graded assessment of changes in calibre, crossing phenomena, reflex changes, generalized vascular constrictions, venular changes, haemorrhages, exudates, stellate figures, papilloedema etc. The findings are entered on a form stamped in the case notes and the total changes are evaluated and classified into stages I II III III-IV and IV. All the cases are assessed individually, paying due regard to age.

Among deviations from the classic grouping it may be mentioned that haemorrhages with vascular changes are placed in group II-III whereas cotton wool exudates always a serious sign are assigned to group III. Like really severe arteriolar changes including generalized severe vascular constriction. Severe vascular changes are listed as "malignant".

It was discussed whether the time had come to omit the word hypertension entirely from the diagnosis as the ophthalmoscopic examination deals more with an evaluation of the condition of the vessels including the degree of arteriosclerosis and permeability. It was suggested to use the term retinal vascular lesion group I-IV possibly abbreviated RVL gr I-IV.

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J. Hvidberg Hansen and F. Erlin Larsen *Congenital Cysts of the Iris* Acta ophthal (Kbh) 50 (1972) 501-514

Discussion: O. A. Jensen

A. Bruun Larsen *Pyruvate and Citrate Concentrations in Bovine Aqueous Humor* Acta ophthal (Kbh) 50 (1972) 470-480

Discussion: O. A. Jensen

Michael Bay *Water Movement and the Vitreous Body*

The water movement in the vitreous body was studied experimentally in the guenon and rabbit by means of fluid scintillation counting using tritiated water as tracer. By comparison with theoretically calculated values for the diffusion of water in a spherical body it was established that more than simple diffusion takes place in the vitreous body.

In another experimental series performed on guenons a fluid flow was recorded by means of microautoradiography on water soluble substances.

Discussion *E Bala : H Ehlers O A Jensen Sv Usterlun S Ry Andersen*

Jens Edmund *Injection of Hyaluronic Acid in the Treatment of Retinal Detachment*

Discussion *B Rosengren K A Dreisler E Bala : E Gregersen S Ry Andersen O A Jensen*

B Rosengren The great contribution to detachment surgery by Gonin is the observation that the sealing of the tear is a necessity in order to reattach the retina. In the common retinal detachment i.e. where one or more tears appear the treatment consists in producing an inflammatory reaction which makes the neuronal layers adhere to the pigmented layers of the retina. In order to obtain such an adhesion the retinal layers have to be close to each other at the point where the tear is located and in the immediate neighbourhood. This means that the subretinal fluid in this area must disappear in most cases the result of an enbuckling procedure.

As a complement to the above mentioned scleral indentation the introduction of different materials into the vitreous may be used. These substances will then seal the tear from the inside. The oldest method of this kind is injection of air. 1 1/2 cc of air being injected into the vitreous cavity. Because of the high surface tension which appears between the air bubble and the fluid the air will act as if it were surrounded by an elastic membrane and hence try to form a sphere. If the eye is oriented in such a fashion that the air bubble is attached to the retinal tear the result will be a sealing effect. This will enhance absorption of the retinal fluid without refilling and improve healing. During the past decade silicon has been used for the same purpose. However as the silicon has a less pronounced surface tension this fluid may slip through the tear into the subretinal space. Injection of saline or similar fluids as blocking agents is of no value.

Injection of hyaluronic acid with its high viscosity is another and new aid. Because of the viscosity the passage through the tear will be very slow and hence increase the healing tendency if injected secondary to the production of adhesive inflammation. It must be borne in mind however that in spite of the high viscosity of the hyaluronic acid the fluid will leak through the tear if the tear is not sealed. Therefore the initial healing reaction must be utilized.

J A Fahmy *Vitreous Haemorrhage Aetiology : Follow up*

The aetiology and clinical features of 26 cases of spontaneous vitreous haemorrhage were reported. Retinal tears were at fault in six cases, retinal periphlebitis in two cases, malignant melanoma and epidural haematoma in one case each, and lastly the aetiology in the remaining 16 cases was assumed to be vasopathy (arteriosclerosis, arterial hypertension). Of the 18 patients seen at follow up 11 exhibited a few float

This mixed stain is contra indicated in conditions in which the connective tissue is denuded of epithelium (deep keratitis corrosion) owing to the risk of a green tattooing of the connective tissue

Reference

Norn M S Vital Staining of Cornea and Conjunctiva Acta ophthal (kbh) Supp 112 (1972) 64 pp

Discussion E Gregersen P M Møller S Ry Andersen

N Ehlers and V A Jensen Fluorescence Angiography of Hereditary Retinal Telangiectasia To be published

Discussion F Krogh

Ordinary General Meeting

M S Norn as Chairman

President's report and treasurer's accounts were adopted N Ehlers was elected Vice President and N Th Rosenberg Secretary

Report from the Committee for the Prevention of Blindness New statutes for the Society were passed

44th Meeting May 6 1972 at Scanticon near Århus

Bjerrum Memorial Lecture

Endre A Balazs (Boston) *The Structure of the Vitreous Body*

45th Meeting May 6 1972 at Scanticon near Århus

Sven Osterlin *Lysosomal Proteases in the Vitreous and Aqueous Humour*

Proteolytic enzymes in aqueous and vitreous from bovine and primate eyes have several properties in common with lysosomal proteases participating in the degradation of proteoglycans

The proteolytic activity of the vitreous is generally higher than in the aqueous suggesting a diffusion of enzymes from the vitreous into the anterior chamber The topical distribution of extracellular protease in the vitreous is correlated to the density of the hyalocyte population

Recent findings by the author indicate the presence of proteoglycans in the juxta canalicular tissue The aqueous must pass the juxta canalicular tissue to gain access to Schlemm's canal The possibility of an interaction between the matrix of this tissue and the proteolytic enzyme of the aqueous was discussed

Discussion E Gregersen E Balazs O A Jensen S Ry Andersen E Godtfredsen

JUDICIA DE NOVIS LIBRIS

Locatcher Khoraiz Deborah & Seegal Beatrice Carrier (eds) Microbiology of the Eye
361 pages with 258 illustrations C V Mosby Co St Louis 1972

This book covers almost every aspect of modern ocular microbiology. The volume is divided into twenty chapters written by sixteen authors well known in their field of research. The first chapter gives the historical background of present knowledge on the subject. The following six chapters cover the field of the bacterial flora of the eye in health and disease as well as postoperative infections and aseptic technique.

The remaining chapters deal with ocular tuberculosis, leprosy, toxoplasmosis, toxocariasis, syphilis and furthermore infections caused by rickettsiae, viruses and fungi.

This book is well written and illustrated. It is to be recommended. *J A Fahmy*

J Haut & S Limon Chirurgie Pratique du Vitre Masson & Cie Paris 1970 134 pages
117 figures Price F Fr 170

This publication marks the beginning of a series of handbooks by La Societe Francaise d'Ophthalmologie on various ophthalmologic disturbances. The vitreous body and its structure, reactions and treatment have become the subject of considerable interest in recent years, not least with regard to the treatment of series of retinal disorders such as retinal detachment and diabetic retinopathy.

The book comprises three sections, the first of which gives a brief review of embryology, anatomy and physiology. This is followed by a section on physiopathology, special attention being devoted to the vitreous body as the producer of the eye's reactions in various mechanical, clinical and biological influences.

Finally comes the actual purpose of the book - a presentation of various surgical means of treating these disturbances. The book ranks among the best in its class; it is concise, is filled with many good illustrations and has numerous English and French summaries which make it exceptionally useful both for the beginner as an introduction to this very pertinent subject and for the teacher as an example of a clear, systematic presentation of the subject.

Jens Edmund

Bitonte J L & Keates R H (eds) Symposium on the Flexible Lens The C V Mosby Company Saint Louis 1972 241 pages Price US \$ 18.85

This publication from the Contact Lens Seminar must be regarded as part of the large and growing interest in flexible lenses which has come about in recent years. The Symposium originated in 1968, however, and with the recent accelerated development of this field, the information reported must be regarded as somewhat outdated today.

The book gives an extremely useful description of the biochemical basis behind the production of the various flexible lenses and concentrates especially on Bausch & Lomb's soft lens, Griffin's biomimetic naturalens and the Muller-Welt silicon rubber lens.

A similarly detailed description is given of the physiologic activities of the cornea and the bases for prescribing flexible lenses. This is followed by a comparison with hard mini lenses and it is of course this section which will be of greatest interest to the clinician.

ing opacities in the vitreous four had moderate opacities and in three cases it was not possible to inspect the retina because of massive opacities. Two patients exhibited retinal degeneration presumably as a consequence of the vitreous haemorrhage. None of the followed patients had elevated tension. To be published.

Discussion A. K. Drisler, J. Edmund, V. Ehlers, B. Rosengren, S. Ry, Andersen, Preben Kristensen, E. Westerlund.

E. Godtfredsen: *Enzymes and Antienzymes in Ophthalmology*

Impressive advances in basic science in recent years, in particular in molecular biology, biochemistry and physiology, are now beginning to benefit ophthalmology. The increasing number of biochemical publications tackling central unelucidated problems such as the aetiology of cataract and glaucoma, retinal perception and transmission are symptomatic. If clinicians are to profit by these new data, they need some kind of biochemical rearmament.

But how?

This is where enzymes come in as an excellent introduction to the biochemical universe. Ophthalmologists are pre-favoured in this respect owing to their daily use of enzymes as well as antienzymes. Enzymes are the dynamic elements of biochemistry, involved in all metabolic steps and in all neuro-transmissions in the eyes and central nervous system. The relationship enzyme-hormones is fairly new and exciting after the demonstration of the adenylyl cyclase system as a "second messenger".

On the basis of these premises it is realized that antienzyme activity may have far-reaching consequences, at worst fatal, but under controlled conditions enzyme blocking or inhibition is of therapeutic value.

A brief orientation of the structure-function-further ecological activity of the enzymes as well as the range of their diagnostic and therapeutic applicability was given.

Enzymes are in a biological key position. Their production is genetically programmed like that of other proteins, but at the same time enzymes are needed for protein synthesis as for other biosyntheses. Enzymes are necessary for the production, action and destruction of neurotransmitters as well as of hormones and thus in a central position in our homeostasis. Among enzyme inhibitors, most interest in ophthalmology attaches to inhibitors of cholinesterase, carboanhydrase and catecholamine oxidases.

It was concluded that in addition to other important activities, enzymes are also able to catalyze clinical ophthalmologists to biochemical rearmament. This will acquire increasing interest in future years in which many new advances could be expected from biochemical physiological research.

Discussion O. A. Jensen.

Knud Rasmussen: *Old Visual Test Types in a New Edition*

Extraordinary General Meeting

Discussion on the recommendations concerning specialist practice submitted by a special committee. An editorial committee was appointed.

The Society is going to apply for membership in the International Association for Prevention of Blindness.

JUDICIA DE NOVIS LIBRIS

Locatcher Khora a Deborah & Seegal Beatrice Carrier (eds) Microbiology of the Eye
361 pages with 738 illustrations C V Mosby Co St Louis 1972

This book covers almost every aspect of modern ocular microbiology. The volume is divided into twenty chapters written by sixteen authors well known in their field of research. The first chapter gives the historical background of present knowledge on the subject. The following six chapters cover the field of the bacterial flora of the eye in health and disease as well as postoperative infections and aseptic technique.

The remaining chapters deal with ocular tuberculosis, leprosy, toxoplasmosis, toxocariasis, syphilis and furthermore infections caused by rickettsiae, viruses and fungi. This book is well written and illustrated. It is to be recommended. / A Fahmy

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117 figures Price FFr 190

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Finally comes the actual purpose of the book - a presentation of various surgical means of treating these disturbances. The book ranks among the best in its class; it is concise, is filled with many good illustrations and has numerous English and French summaries which make it exceptionally useful both for the beginner as an introduction to this very pertinent subject and for the teacher as an example of a clear, systematic presentation of the subject. Jens Edmund

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The book gives an extremely useful description of the biochemical basis behind the production of the various flexible lenses and concentrates especially on Bausch & Lomb's soft lens, Griffin's bionite naturalens and the Müller-Welt silicon rubber lens.

A similarly detailed description is given of the physiologic activities of the cornea and the bases for prescribing flexible lenses. This is followed by a comparison with hard minilenses and it is of course this section which will be of greatest interest to the clinician.

The problem of lens contamination and sterilisation is of considerable significance for flexible lenses but the prevalent risks regarding bacterial absorption and fungus infection are rejected

The advantage of flexible lenses is not least to be found in the fact that they are easy to accept and that they do not require the annoying maintenance that so often accompanies hard contact lenses

At the same time however not everyone finds flexible lenses equally easy to accept and many patients complain of stinging and irritation with soft lenses

The primary use is and presumably will remain therapeutic - i.e. the bandage lens. As mentioned we find ourselves at the dawn of a new day in eye care and a new method which seems to promise many rich possibilities has been devised

One can expect that the many sidedness of the hydrophilic lens will make it a routine therapeutic method in future ophthalmologic practice.

Jens Edrúnd

Iris Lucien Histopathologie Oculaire Masson et Cie Paris 1972 262 pages 151 figures
Price F Fr 180

The book is aimed directly at practicing ophthalmologists and pathologists and uses clear easily understandable language The embryology anatomy and physiology of the eye are reviewed briefly and schematically and special technical terms are defined in a glossary Rare illnesses are omitted and (unfortunately) so are etiology and pathogenesis

Such a concise book must naturally lack a great deal of what the ophthalmopathologist might hope to find and the classification of tumors is not in accordance with the generally recognized international classification As a whole however the book achieves its intended purposes and the numerous black and white photos will be of help to the reader

S Ry Andersen

Capella J A Edelhauser H F & van Horn D L Corneal Preservation Clinical and Laboratory Evaluation of Current Methods Charles C Thomas Springfield Illinois Price \$ 22 50

Methods of corneal preservation have remained essentially the same for decades but recently the increasing demand for corneal tissue for transplantation has encouraged the development of better methods of short term and long term preservation The present volume summarizes the proceedings of a symposium held in Gainesville Florida in December 1970

The various aspects of corneal preservation are discussed in the 50 chapters The difficulties in obtaining human tissue and the problems involved in short term preservation appear to vary from country to country The value of the publication of the papers read at a symposium held almost three years ago is only that it provides a complete survey of the problems Many of the papers have already appeared in more or less the same shape in the regular journals

To the reviewer the chapters on cryopreservation seem to be the most interesting It should now be evident that it is possible to use cryopreserved tissue and the results are comparable to those obtained with fresh tissue

The book can be warmly recommended to those engaged in research on corneal grafting
Niels Ehlers

Motokawa K. *Physiology of Color and Pattern Vision* Igaku Shoin Ltd Tokyo Springer Verlag Berlin - Heidelberg - New York 1970 283 pages 137 figures 26 tables US \$ 18.00

This monography presents a survey of studies done during the past twenty five years in the Dept. of Physiology Tohoku University under the leadership of the late Prof Motokawa

The activities of this laboratory have in particular been concerned with the electric phosphenes which are subjective phenomena induced by electrodes placed on the head. The thresholds of these phosphenes are influenced by previous illumination of the retina and interestingly enough by the wavelength of the radiation. A method has thus been developed which is useful in studies of perception of psychophysical phenomena in animals as well as in man.

The electrical excitability of the retina is a helpful instrument when dark adaptation, colour perception, lateral inhibition, contrast sensitivity, optical illusions, movement sensation and stereoscopic vision are concerned. The application of the author's method is instrumental in filling the gap between physiology and psychophysics as it is demonstrated by well documented data.

Furthermore the book gives a comprehensive synopsis of our previous knowledge of visual physiology to be discussed in the light of the author's theory. The methods described are immature for clinical application but the book can be recommended to everybody interested in visual physiology and visual perception.
V. Dreyer

Stimson Russel L. *Ophthalmic Dispensing* 2nd ed. Charles C Thomas Springfield Ill 1971 604 pages 933 figures US \$ 9.50

In English speaking countries a distinction between two groups of opticians is drawn: refracting opticians (further developed into optometrists) and prescription opticians or dispensing opticians, the latter group being more closely related to medicine. The education of these two groups follows separate tracks and many states have ascertained their individual rights in legislation.

The present book addresses itself to all students of ophthalmology. The author, who is the president of a Californian Optical Society, has a well established background as a teacher.

An easily read and fluent presentation introduces the reader to the items of geometrical optics: ophthalmic lenses including bifocal and multifocal lenses, cataract lenses, vocational lenses, subnormal vision lenses, evaluation of glasses and fitting and adjusting of the frames.

The text is charged with practical advice and ethical considerations and is relievingly devoid of scanty theories.

It could be recommended to all postgraduate students of ophthalmology and to ophthalmologists interested in refraction practice. On one hand technical errors are prevalent causes of a patient's refusing a correct prescription and on the other hand the technical potential should be familiar to all refraction practitioners.
V. Dreyer

VARIA

The National Eye Research Foundation Chicago Illinois and the Contact Lens Society of Great Britain

Announcing an International Contact Lens Congress to be held in Montreux Switzerland on August 10-12, 1974. The Congress is being co-sponsored by the National Eye Research Foundation and the Contact Lens Society of Great Britain. Details regarding the meeting can be obtained from the National Eye Research Foundation, 18 South Michigan Avenue, Chicago, Illinois 60603. Tel. (312) 726-7866.

Symposium on Ocular Motility

A Wenner Gren Center International Symposium on *Basic Mechanisms of Ocular Motility and Their Clinical Implications* will be held in Stockholm, Sweden, on June 4-5, 1974. For further information, write: Wenner Gren Center Symposium Secretariat, Svcavagen 166, S-113 46 Stockholm, Sweden.

Ophthalmic Plastic Surgery

The Pagen and William Black Post Graduate School of Medicine of the Mount Sinai School of Medicine of the City University of New York announces a Post Graduate course in Ophthalmic Plastic Surgery under the direction of Virginia Lubkin, MD, FACS; David B. Soll, MD; Pierre Guibor, MD; Donald Wood Smith, MD; Morris Feldstein, MD, FACS; Murray A. Meltzer, MD. February 21 and 22, 1974, 9:00 a.m. to 5:00 p.m. (two sessions) at the Mount Sinai Medical Center, Fifth Avenue and 100th Street, New York, N.Y. 10029. For catalogue and applications, write: Registrar, The Pagen and William Black Post Graduate School of Medicine, Mount Sinai School of Medicine, Fifth Avenue and 100th Street, New York, N.Y. 10029. Tel. (212) 916-1000, extension 8384.

The Twelfth ISCLRG Symposium

(International Society of Clinical Electrophysiology) will take place in Clermont Ferrand, France, May 20 to 22, 1974. The main topics will be: "Exploration of macular function and fundamentals of the mathematical analysis of electrophysiological waveforms." The registration fee is 200 FF for ISCLRG members (250 FF for non-members and 150 FF for accompanying persons). Registration proposals for papers (10 minute presentations, 250 word abstracts) and room reservations (from 10 FF to 160 FF) will be accepted till February 15, 1974, at the latest. Mailing address: Professor P. Solé, ISCLRG Symposium 1974, Clinique ophtalmologique, Hôpital Saint Jacques, 30 Place Henri Dunant, 63001 Clermont Cedex (France).

